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The Association Between Blood Lead Level and Microcytic Hypochoromic Anemia in Children

Soheila Zareifar,[1] Samaneh Mazloomi,[2] Mozhgan Zahmatkeshan,[2] Mahdi Shahriari,[1] Khadijeh Saadat Najeeb,[2,*] and Fahimeh Fattah[2]

[1]Hematology Research Center, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, IR Iran
[2]Department of Pediatrics, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, IR Iran

[*]*Corresponding author*: Khadijeh Saadat Najeeb, Department of Pediatrics, Shiraz University of Medical Sciences, Shiraz, IR Iran. Tel.: +98-9175550409, E-mail: nikaeinf@sums.ac.ir

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Abstract

Background: Iron deficiency, as the most common nutritional deficiency, often occurs in the pediatric age group due to rapid growth and low dietary iron content.
Objectives: The present study aimed to assess the relationship between microcytic hypochromic anemia and blood lead level below the standard acceptable upper range in children aged between one and ten years.
Methods: In this study, 27 cases, who fulfilled the inclusion criteria were assigned to group A, as hypochromic microcytic anemia with iron deficiency. Another 18 hypochromic microcytic anemia cases with normal ferritin levels were assigned to group B. Besides, 20 healthy children were chosen as the control group. All the statistical analyses were performed using the SPSS statistical software. P values of < 0.05 were considered to be statistically significant.
Results: The children in group A showed significant correlations between lead levels and hemoglobin (-0.770; P values = 0.001), mean corpuscular volume (MCV) (-0.679; P values = 0.001), and ferritin (-0.509; P values < 0.001). In group B, only a significant correlation was observed between lead levels and ferritin (-0.637; P values = 0.001). In the control group, a significant correlation was found between lead levels and MCV (-0.483; P values = 0.031) and ferritin (-0.562; P values = 0.010). Multiple comparisons test showed significant mean differences ($\pm$ SD) between the control group and groups A (1.26 ± 0.28; P values = 0.001) and B (1.78 ± 0.31; Pvalues = 0.001) regarding the lead levels, but no significant difference was seen between groups A and B in this regard.
Conclusions: Our study results imply that there is no secure threshold for blood lead level at which, lead begins to cause interruption with hematologic parameters in young children.

Keywords: Lead, Iron Deficiency, Microcytic Hypochromic Anemia, Pediatric

1. Background

Iron deficiency, as the most common nutritional deficiency, often occurs in the pediatric age group due to rapid growth and low dietary iron content (1, 2). Inadequate dietary intake of iron results in excessive absorption of heavy metals, such as lead ions. Concomitant lead toxicity and iron deficiency has been investigated in many studies (3, 4). Some studies revealed that intestinal divalent metal transporter 1 (DMT1), which binds to iron and lead has an important role; therefore, it's expression is modulated by ferritin (5, 6). In low ferritin levels, DMT1 binds to lead, subsequently increasing the lead blood level.

Lead poisoning results from contaminated soil and water or air pollution. It results in adverse interaction in cellular biochemical reactions, leading to many organ and physiological dysfunctions (7, 8). The cut-off point of blood lead concentration to detect lead poisoning has been debated for many years to start from 60 mcg/dL, but recede to 10 mcg/dL after that 3. In January 2012, centers for disease control and prevention (CDC) changed its "blood lead level of concern" from 10 to 4.5 mcg/dL of lead in blood (9). Nevertheless, no exact safe level has been yet established due to the results of studies indicating biological toxicity of even low doses of lead exposure (10-12).

Although the CDC's current definition announced lead blood levels above 4.5 mcg/dL as lead poisoning, it has no specific signs or symptoms and is also hard to diagnose in medical history or physical examinations (13). Mild lead poisoning may cause heme synthesis defect. Thus, chronic exposure to lead may result in anemia (8). Lead can also inhibit the activity of sulphydril group (SH) of enzymes involved in heme synthesis. Therefore, lead poisoning decreases Hemoglobin (Hb) content of red blood cells (RBCs) independently (7). On the other hand, increased blood levels of lead may inhibit protoporphyrin synthesis, a precursor of heme. Considering decreased iron absorption caused by lead, even low levels of blood lead, together with lowered heme synthesis in children, may deteriorate anemia. Hence, when two independent causes of anemia, which are also related to each other; i.e., lead poisoning and iron deficiency, occur in an individual simultaneously, the outcomes will be remarkably worsened (14).

Hypochromic microcytic anemia is defined as reduction in red blood cell (RBC) mass or blood Hb concentration combined with mean corpuscular volume (MCV) values less than 2 SD, below the mean references (7). Microcytic anemia could be the result of iron deficiency, chronic diseases, and also lead poisoning (15).

There is an ongoing debate over the effects of even low blood lead levels on children with anemia. However, most studies have not revealed whether the preceding cause is either low intake of iron or over exposure to lead. Therefore, the association between blood lead concentrations and iron deficiency concomitant disorder in children is controversial (13, 16, 17).

2. Objectives

Moreover, because of the alarming prevalence of iron deficiency and blood lead levels, we decided to assay the association between below 5 mcg/dL blood lead levels (which is considered to be within the safe range) and anemia-related parameters, such as MCV and Hb.

3. Methods

3.1. Patient Selection

This cross-sectional study was performed on children referred to the pediatric hematology clinics affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. Patient screening was conducted from May 2013 to August 2013. New cases of microcytic hypochromic anemia were recruited from the screening program. All the patients had mean Hb and mean MCV levels lower than the normal range for their gender and age stratified cut-off values according to diagram references from CDC, recommendations to prevent and control iron deficiency in the United States, April 1998 (2). The inclusion criteria of the study were having microcytic hypochromic anemia and being in the age range of one to ten years. On the other hand, the exclusion criteria were having above 5 mcg/L blood lead level, internal organs dysfunction, administration of any kind of iron or vitamin therapy three months before the beginning of the study, having had any active inflammatory or infectious diseases two weeks prior to the study initiation, and history of preterm birth or low birth weight.

In addition, the control group included children with no history of any type of anemia during the previous three months, who had normal Hb, MCV, and ferritin levels, according to the reference diagram in the study screening program.

At first, the research aims were explained to the participants' parents and then, all the parents signed a written informed consent. Moreover, they were assured of the confidentiality of their data and their right to withdraw from the study if they were not willing to continue. All the participants were examined by a physician and a nutritionist, at the beginning of the study. This study was approved by the ethics committee of Shiraz University of Medical Sciences (Code: 5033).

3.2. Sample Collection

Blood sample collection and anthropometric assessments were done for all the subjects. A 2-mL blood sample was collected for each patient in clot tubes for lead and ferritin measurements using a lead-free venous blood collection kit. All the samples were centrifuged at 2500 rpm at 4°C for 10 minutes. After separation, the sera were stored at -80°C until assay. Another 2 mL of blood was collected in EDTA containing tubes for complete blood count (CBC) test. The serum concentrations of ferritin were measured using the automated Elecsys 2010 Immunoanalyzer Hitachi/Roche Diagnostic System. Besides, CBC was counted using automated hematology analyzer (Sysmex hematology analyzer, model XS800 I, Japan). Blood lead levels were also measured using flameless graphite furnace atomic absorption spectrophotometry (AAS) (Perkin Elmer Model 4100ZL, Norwalk, CT) by the standard addition method. The method's detection limit of blood lead concentration was 0.05 mcg/dL.

Anthropometric measurements, including weight, height, and Body Mass Index (BMI), age, gender, and living area, were recorded, as well.

3.3. Statistical Analysis

All the statistical analyses were performed using the SPSS statistical software, v. 20.0 (SPSS Inc., Chicago, IL). P values of < 0.05 were considered to be statistically significant. The results were expressed as mean $\pm$ standard deviation (SD) or mean changes (95% CI). At first, One-Sample Kolmogorov-Smirnov normality test was performed to confirm normal distribution of the data. Additionally, multiple logistic regression analysis was used to test the association between blood lead level and various CBC values described in the succeeding sections.

4. Results

4.1. Patients' Characteristics

After screening more than 200 children, who had been referred to the pediatric hematology clinics affiliated to Shiraz University of Medical Sciences, 45 cases who fulfilled the inclusion criteria were assigned to groups A (n = 27) and B (n = 18). Healthy children, who did not show any signs of anemia with normal serum ferritin and hemoglobin levels, were also enrolled in the control group (n = 20). The male/female ratio was 31:34 in the total participants. The characteristics of the study children are presented in Table 1. Also no significant differences were seen amongst the three groups after performing one-Sample Kolmogorov-Smirnov normality test for age and body mass index (BMI).

Because all the microcytic hypochromic patients did not have ferritin levels lower than normal ranges according to their gender and age using cut-off values from the CDC references diagram, we divided the patients to two groups of above and below 15 ng/dL ferritin levels. Lead blood level was also assessed in the patients with normal store of iron (ferritin) who suffered from microcytic hypochromic anemia.

4.2. Blood lead, serum ferritin, hemoglobin, and Mean Corpuscular Volume

The correlations between the main parameters in the three groups are shown in Table 2. Accordingly, the children in group A showed significant correlations between lead levels and hemoglobin (-0.770; $P < 0.01$), MCV (-0.679; $P < 0.01$), and ferritin (-0.509; $P < 0.05$). In group B, only a significant correlation was found between lead levels and ferritin (-0.637; $P < 0.01$). In the control group, a significant correlation was observed between blood lead levels and MCV (-0.483; $P < 0.05$) and ferritin (-0.562; $P = 0.01$). Multiple comparisons Tukey's Post Hoc test (Table 3) showed significant mean differences ($\pm$ S.D) between the control group and groups A (1.78 ± 0.31; $P < 0.01$) and B (1.26 ± 0.28; $P < 0.01$) regarding the lead levels, but no significant difference was seen between groups A and B in this respect. Besides, no significant difference was observed among the three groups with regards to the secondary parameters, including gender and body mass index (BMI). The results also showed no significant relationship between the secondary parameters, including gender and BMI, and blood lead levels in the three groups. However, the blood lead levels were higher among the children living in urban areas (0.99 ± 0.27; $P = 0.001$) compared to those living in rural areas (data not shown).

5. Discussion

Anemia is the most known health-threatening result of lead toxicity. However, controversial associations between blood lead concentrations and iron deficiency have been found in different studies (8, 10, 17, 18). The present study aimed to assess the relationship between microcytic hypochromic anemia and low lead blood levels in children aged between one and ten years.

Our study results showed that the serum lead levels were significantly higher in anemic children of both case groups compared to the non-anemic children in the control group. A possible explanation is that inadequate iron stores, which are a proven cause of anemia, initiate signals, which result in increased intestinal absorption and possibly retention of divalent metals, such as Pb^{++} in the body (18).

Aminolevulinic acid dehydratase (ALAD) and hemechelatase activity, the most important enzymes participating in heme synthesis, have been shown to be inhibited by lead (19). Most of the blood circulating lead is found in erythrocytes because of their high affinity for lead (20). Cellular damage could happen after peroxidation of erythrocyte membrane lipids and oxidants initiated by ferrous ion stimulation associated with lead intoxication (21, 22). In addition to shortening the life span of blood cells and interrupting normal cellular function, lead can lower cellular concentrations of reduced Glutathione (GSH), thus reducing the redox buffering capacity of cells (23). Glutathione has a reactive thiol group (-SH) and acts as a non-enzymatic detoxification cofactor for free radicals as well as heavy metals (24).

The results of the present cross-sectional study showed a strong negative dose-response association between blood lead concentrations and some hematologic parameters, which is in agreement with many previous findings (8, 10, 13, 25). Three situations could be imagined for the obtained results in the three groups. Situation one; in group A with iron deficient microcytic anemia children, iron deficiency with or without higher exposure to environmental lead caused mean blood lead levels of 2.49 ± 1.13 mcg/dL. This group possessed the highest mean blood lead concentration, which significantly resulted in decreased MCV and Hb. However, like many other cross-sectional studies, the question is which one was the first, iron deficiently or high lead exposure. Therefore, stronger longitudinal clinical trials should be conducted on the safe limit of blood lead concentration to better determine the priority of causes and effects. Park et al. performed a trial on iron deficient infants and revealed that after iron supplementation, lead levels decreased significantly even in infants with low lead concentrations (26). Nonetheless,

Table 1. Characteristics of the Study Subjects in the Case and Control Groups[a]

	Group A	Group B	Control	P Value
Age, y	3.29 ± 2.71	2.76 ± 2.33	5.03 ± 3.47	0.316
BMI, kg/m^2	18.29 ± 2.74	16.48 ± 1.20	16.82 ± 1.51	0.421
Hemoglobin, g/dL	10.60 ± 0.82	9.71 ± 1.04	13.25 ± 0.82	-
MCV, fL	70.96 ± 4.53	66.32 ± 7.04	84.95 ± 3.84	-
Ferritin, ng/dL	9.11 ± 3.74	65.55 ± 23.42	87.15 ± 39.64	-
Serum lead level, mcg/dL	2.49 ± 1.13	1.97 ± 1.02	0.71 ± 0.33	-
N (Male/Female)	27 (16:11)	18 (10:8)	20 (8:12)	-

Abbreviations: BMI, body mass index; MCV, meancorpuscular volume; group A, hypochromic microcytic children with iron deficiency; group B, hypochromic microcytic children with normal ferritin levels.
[a]Values are expressed as mean ± SD.

Table 2. The Correlations Between Serum Lead Levels and Hemoglobin, Mean Corpuscular Volume, and Ferritin in Each Group

	Lead levels			P Value
	Group A	**Group B**	**Control**	
Hemoglobin concentration				
Group A	-0.770	-	-	0.001
Group B	-	-0.325	-	0.092
Control	-	-	0.297	0.242
MCV levels				
Group A	-0.679	-	-	0.002
Group B	-	-0.534	-	0.084
Control	-	-	-0.483	0.031
Ferritin concentration				
Group A	-0.509	-	-	< 0.001
Group B	-	-0.637	-	0.001
Control	-	-	-0.562	0.010

Abbreviations: MCV, mean corpuscular volume; group A, hypochromic microcytic children with iron deficiency; group B, hypochromic microcytic children with normal ferritin levels.

some studies have found that this relationship is only possible at high concentrations of blood lead (8, 10, 25).

Situation two can be imagined for the cases in group B. The children in this group had acceptable ferritin levels for their ages, but they were known cases of microcytic anemia. Levels of ferritin in this group were lower than those of the control group, resulting in more absorption of lead and mean lead blood level of 1.97 ± 1.02 mcg/dL. Yet, the relationship between blood lead levels and hematologic parameters was only significant for ferritin. This condition could be explained only when these participants suffer from some kinds of genetic or physiologic disorder in heme synthesis, which was not tested in the current study. Another explanation is unknown confounders. These conditions may result in MCV or Hb reduction independently from lead pathways, thereby interrupting the relationship. It may also reflect other nutrient deficiencies at this sensitive age. Wolf et al. (13) in their study on iron depletion in infants showed that correcting body iron status corresponded closely to changes in lead levels. However, Serwint et al. (17) found no correlations between iron and lead concentrations in the absence of iron deficiency. The third situation belongs to children in the control group, non-anemic children whose mean blood lead level was 0.71 ± 0.33 mcg/dL. Normal iron stores with or without low environmental lead exposure could result in lower absorption of lead in GI and, consequently, lower concentration of Pb^{++} in the circulating blood.

Table 3. Lead Levels and Body Mass Index Mean Differences Using Multiple Comparisons Post Hoc Test

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J) ± S.E.	P Value	95% CI
Lead levels, mcg/dL	Group A	Group B	-0.52 ± 0.29	0.188	-1.2274 - 0.1852
	Group A	Control	1.78 ± 0.31	< 0.001	1.0293 - 2.5375
	Group B	Control	1.26 ± 0.28	< 0.001	0.5775 - 1.9471
BMI, kg/m^2	Group A	Group B	1.80 ± 0.62	0.115	0.298 - 3.316
	Group A	Control	1.47 ± 0.60	0.048	0.008 - 2.934
	Group B	Control	-0.33 ± 0.67	0.871	-1.947 - 1.275
Hemoglobin, g/dL	Group A	Group B	0.88 ± 0.27	0.005	0.237 - 1.537
MCV, fL	Group A	Control	4.64 ± 1.57	0.012	0.860 - 8.422

Abbreviations: BMI, body mass index; MCV, meancorpuscular volume; group A, hypochromic microcytic children with iron deficiency; group B, hypochromic microcytic children with normal ferritin levels.

The regression models obtained from our results revealed a significant correlation between Hb level and blood lead level (β = -0.99 ± 0.25; P < 0.01). Froom et al. (27) also suggested that anemia was not related to low levels of blood lead. In a study by Drossos et al. (28), children with blood lead levels of > 30 mcg/dL showed a linear decline in Hb levels.

The present study results indicated that even below 5 mcg/dL lead levels in children could increase the risk of anemia and negatively affect some hematologic parameters. Furthermore, higher levels of blood lead were associated with lower levels of blood ferritin.

5.1. Conclusions

Our study results imply that there is no secure threshold for blood lead level at which, lead begins to cause interruption with hematologic parameters in young children. Therefore, the blood lead level currently considered by CDC as a safe margin should be replaced with the phrase "as less as possible". Our results also indicated that treatment of iron deficiency anemia might be an effective preventer of infant lead toxicities, even in non-anemic children. Thus, serious efforts are needed to continue to reduce infants' exposure to this inevitable environmentally toxic heavy metal.

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Footnotes

Authors' Contribution: Study concept and design: Soheila Zareifar and Khadijeh Saadat Najeeb; acquisition of data: Samaneh Mazloomi; analysis and interpretation of data: Mozhgan Zahmatkeshan and Samaneh Mazloomi; drafting of the manuscript: Mahdi Shahriari and Mozhgan Zahmatkeshan; administrative, technical, and material support: Shahriari Mahdi; study supervision: Khadijeh Saadat Najeeb and Soheila Zareifar; critical revision of the manuscript for important intellectual content: Khadijeh Saadat Najeeb.

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