Association Between Iron Deficiency and Low-Level Lead Poisoning in an Urban Primary Care Clinic

Robert O. Wright, MD, Michael W. Shannon, MD, MPH, Rosalind J. Wright, MD, MPH, and Howard Hu, MD, ScD

ABSTRACT

Objectives. The purpose of this study was to examine the association between iron deficiency and low-level lead poisoning.

Methods. Data were collected in an urban primary care clinic from 3650 children aged 9 to 48 months. Iron deficiency was defined as a red cell mean corpuscular volume (MCV) of less than 70 fL and a red cell distribution width (RDW) of more than 14.5 in children younger than 2 years, and an MCV of less than 73 fL and RDW of more than 14.5 in those 2 years or older.

Results. After adjustment for age, hemoglobin concentration, and insurance status, the odds ratios for iron deficiency predicting blood lead levels greater than or equal to 5 μg/dL and greater than or equal to 10 μg/dL were 1.63 (95% confidence interval [CI] = 1.29, 2.04) and 1.44 (95% CI = 1.004, 2.05).

Conclusions. Iron deficiency is significantly associated with low-level lead poisoning in children aged 9 to 48 months. (*Am J Public Health.* 1999; 89:1049–1053)

Iron deficiency is the most common nutritional problem among children worldwide, and lead toxicity is the most common environmental health threat to children. Both iron deficiency and lead poisoning disproportionately affect children younger than 5 years, those of lower socioeconomic status, and those living in inner cities.[1,2] Previous studies suggest a strong link between iron deficiency and blood lead levels greater than 30 μg/dL, which was the level used to define lead poisoning before 1986.[3,4] Since then, the definition of lead poisoning has been adjusted on the basis of scientific evidence suggesting that lead affects neurocognitive development at blood levels as low as 10 μg/dL.[5]

Currently, the vast majority of US children who have lead poisoning have blood lead concentrations of 10 to 30 μg/dL.[2,6] Furthermore, although it has since been replaced by direct measurement of the whole-blood lead concentration, erythrocyte protoporphyrin concentration was used until 1991 to screen children for lead poisoning.[7] Because lead poisoning resembles iron deficiency in that it increases erythrocyte protoporphyrin concentration, use of the latter measure may have created a selection bias in previous studies for patients with both conditions.

Although evidence exists that iron status and low-level lead burden are associated among adults,[8] no previous study of children has demonstrated an association between iron deficiency and low-level lead poisoning as currently defined. To determine whether low-level lead poisoning and iron deficiency are associated, we conducted a cross-sectional study among children being screened for lead exposure on the basis of their blood lead concentration.

Methods

Study Population

The study examined screening data from the outpatient primary care clinics of the Boston Children's Hospital from January 1994 to December 1996. Children seen in this clinic live primarily in an urban setting. The study population consisted of children aged 9 to 48 months who were followed up over a 3-year period for primary care. Massachusetts state law mandates that all children be screened for lead poisoning beginning at 9 to 12 months of age and annually thereafter until 4 years of age. Children at the clinic are also routinely screened annually for anemia, through complete blood cell counts (CBCs). During the study period, measurements of venous whole-blood lead concentration and complete CBCs were made to screen for lead poisoning and anemia, respectively.

Iron Deficiency Criteria

Iron deficiency was defined according to American Academy of Pediatrics criteria

Robert O. Wright, Rosalind J. Wright, and Howard Hu are with the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass. Robert O. Wright is also with the Department of Pediatrics, Brown University Medical School, Providence, RI, and Howard Hu is also with the Occupational Health Program, Department of Environmental Health Sciences, Harvard School of Public Health, Boston. Michael W. Shannon is with the Department of Medicine, Boston Children's Hospital, Harvard Medical School.

Requests for reprints should be addressed to Robert O. Wright, MD, Channing Laboratory, 181 Longwood Ave, Boston, MA 02115 (e-mail: robert.wright@channing.harvard.edu).

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for mean corpuscular volume (MCV) and red cell distribution width (RDW). Children younger than 2 years were classified as iron deficient if they had an MCV of less than 70 fL and an RDW of more than 14.5; children 2 years or older were considered iron deficient if they had an MCV of less than 73 fL and an RDW of more than 14.5.[9,10] A definition based on such established criteria is useful in identifying patients with early iron deficiency who are not yet anemic and has been shown to better distinguish heterozygous thalassemia and anemia of chronic disease from early iron deficiency.[10–12]

Insurance Status

Information on date of birth and insurance status of children was collected during registration for each clinic visit. Studies have shown that insurance status is associated with household income,[13–15] and insurance status is commonly used as a marker of socioeconomic status.[13] Insurance status was divided into 3 categories: MassHealth (Medicaid), self-pay, and private insurance.

Analysis of Samples

A sample of venous blood was collected for both measurement of lead and CBC. Samples for blood lead determination were drawn into a 2-mL vacutainer (Becton Dickinson, Franklin Lakes, NJ) containing lithium heparin (45 US Pharmacopoiea [USP] units) (Becton-Dickinson, Inc, Franklin Lakes, NJ), and those for CBC into a 2-mL vacutainer containing K_3EDTA (7.5%, 0.04 mL). All samples were analyzed with a Microdiff 16 hematology analyzer (Coulter, Inc, Miami, Fla) in the clinical laboratory of the Children's Hospital to determine hemoglobin concentration, red cell MCV, and RDW. The whole-blood lead concentration was measured with an atomic absorption spectrometer (Model 5000, Perkin Elmer, Inc, Norwalk, Conn). According to the laboratory's protocol, blood lead concentrations between 0 and 4 μg/dL are reported as less than 5 μg/dL. During the study period, the laboratory participated in the Centers for Disease Control and Prevention (CDC) blood-lead quality assurance program without having any measurements that fell outside the program limits and with an intraclass coefficient of correlation of 0.999 between its measurements and the CDC standards.

Statistical Analyses

Univariate analyses were performed to examine the associations among age, iron deficiency, insurance status, and hemoglobin as predictors of blood lead concentration. Categorical variables were assessed with the χ^2 test with correction for continuity, and continuous variables were assessed with the Student *t* test for unpaired data. Odds ratios (ORs) and confidence intervals (CIs) were used to assess the degree of association between blood lead and iron deficiency at the 2 blood-lead cutpoints of 5 μg/dL (0.24 μmol/L), the lower limit of blood lead levels that must be reported to the Massachusetts State Health Department, and 10 μg/dL (0.48 μmol/L), the lower limit defined by the CDC as indicating lead poisoning.[7]

Unconditional logistic regression analysis was used to control for potential confounding of the relationship between blood lead concentration and iron deficiency. In this analysis, the 2 blood-lead cutpoints of 5 μg/dL and 10 μg/dL were used as the dependent variables, with indicator terms for iron deficiency and insurance status (with privately insured patients as the reference group) and continuous terms for age and hemoglobin concentration entered into the logistic model.

TABLE 1—Selected Demographic Characteristics and Laboratory Measures of Study Population

Variable	Mean ± SD	Range	n (%)
Age, y	2.0 ± 1.0	0.75–4.0	
Hemoglobin, g/dL	11.4 ± 0.9	6.3–14.9	
MCV, fL	75.9 ± 5.1	50.4–94.4	
RDW	14.2 ± 1.3	11.6–22.9	
Insurance status			
MassHealth			2243 (61.5)
Private insurance			914 (25.0)
Self-pay			493 (13.5)
Iron status			
Iron replete			3289 (90.1)
Iron deficient			361 (9.9)

Note. Iron deficiency is defined as an MCV < 70 and RDW > 14.5 for children younger than 2 years and an MCV < 73 and RDW > 14.5 for those 2 years or older. MCV = mean corpuscular volume; RDW = red blood cell distribution width; MassHealth = Medicaid.

Results

During the study period, 3650 children were screened for lead poisoning and iron deficiency. Selected demographic characteristics and laboratory data for these children are provided in Table 1. Of the 3650 children who were screened, 361 (9.9%) were iron deficient as defined by MCV and RDW, and 343 (9.4%) had lead poisoning as defined by a blood lead concentration of 10 μg/dL or greater. Among children with lead poisoning, 11.6% were iron deficient. The blood lead concentration ranged from less than 5 μg/dL to 44 μg/dL (0.24–2.12 μmol/L) (Figure 1). More than 50% of the children who were screened had blood lead concentrations below the reporting limit of the laboratory (5 μg/dL [0.24 μmol/L]). The median blood lead concentration was less than 5 μg/dL (range, <5 μg/dL–44 μg/dL). This finding is consistent with the recent finding of the National Health and Nutrition Examination Surveys (NHANES) that 67% of all children in the United States have blood lead concentrations of less than 5 μg/dL.[6]

The distribution of blood lead concentration is illustrated in Figure 1. This distribution, although skewed, is similar to that found for blood lead concentration in the NHANES.[6] Because more than half the children screened had blood lead concentrations reported as less than 5 μg/dL, linear correlations of blood lead as the dependent variable with other variables could not be performed. Blood lead levels were therefore stratified into the 3 categories of less than 5 μg/dL, 5 to 9 μg/dL, and 10 μg/dL or more (<0.24, 0.24–0.43, and ≥ 0.48 μmol/L), which were chosen to coincide with the limits and range of the logistic regression analysis. A breakdown of blood lead concentration according to these values, stratified by age, hemoglobin, MCV, RDW, insurance status, and iron status, is given in Table 2.

Chi-square analysis of the data given in Table 2 showed a significant association between rising blood lead concentration and iron deficiency as defined by the criteria described earlier ($P = .001$). Analysis of variance (ANOVA) and χ^2 tests of selected risk factors with respect to blood lead concentration showed significant differences for age, MCV, and insurance status. In group comparisons, the mean ages of patients with blood lead levels of less than 5 μg/dL and 10 μg/dL or more differed significantly from each

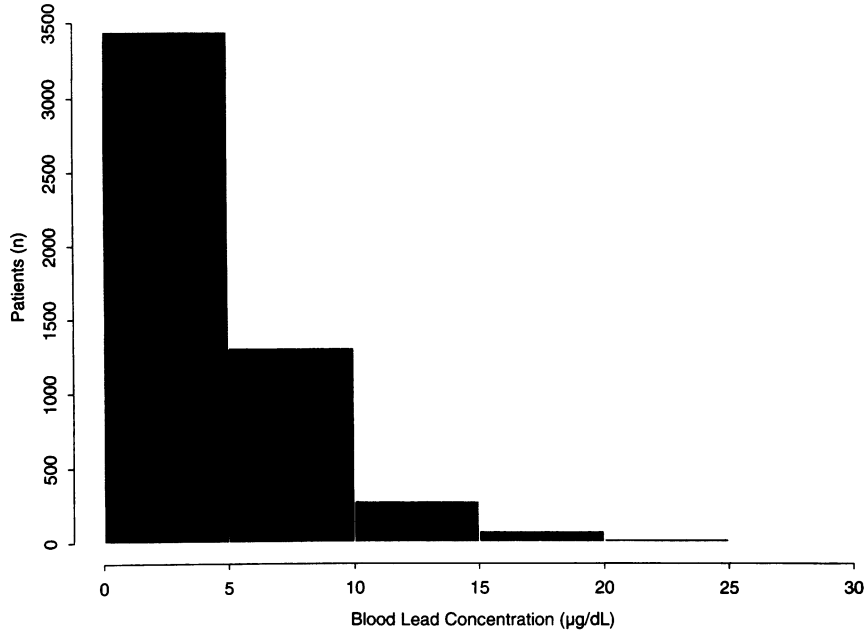

FIGURE 1—Distribution of blood lead concentration among 3650 children screened for lead poisoning. Range, <5 to 44 μg/dL.

other, as did those of patients with blood lead levels of less than 5 μg/dL and 5 to 9 μg/dL ($P = .0001$ in both cases). In contrast, no significant difference in mean age was found for patients with blood lead levels of 5 to 9 μg/dL and those with blood lead levels of 10 μg/dL or more ($P = .92$). However, the MCVs of the patients in all of these groups differed significantly from one another ($P = .0001$, .0001, and .04, respectively).

Univariate analysis of iron deficiency with respect to blood lead concentration showed that the crude odds ratio for iron deficiency predicting a blood lead concentration of 5 μg/dL (0.24 μmol/L) or more was 1.50 (95% CI = 1.20, 1.86). The crude odds ratio for iron deficiency predicting a blood lead concentration of 10 μg/dL (0.48 μmol/L) or more was 1.31 (95% CI = 0.93, 1.84). With control for age, hemoglobin, and insurance status in the logistic regression model, the adjusted odds ratios were 1.63 (95% CI = 1.29, 2.04) for a blood lead concentration of 5 μg/dL (0.24 μmol/L) or more and 1.44 (95% CI = 1.004, 2.05) for a blood lead concentration of 10 μg/dL (0.48 μmol/L) or more among iron-deficient patients. The full results of the logistic regression modeling are shown in Table 3.

Discussion

The results of this study indicate that the combination of increased RDW and decreased MCV is associated with blood lead concentrations of more than 5 μg/dL (0.24 μmol/L) and 10 μg/dL (0.48 μmol/L). The study shows that iron deficiency is associated with even the lower blood lead concentrations currently found in the US population. However, the association is not as strong as reported in studies of children with moderate to severe lead poisoning. Clark et al. reported that more than 50% of children hospitalized for severe lead poisoning (blood lead concentration > 70 μg/dL) had evidence of iron deficiency.[4] Yip et al. reported that 86% of children with blood lead levels of less than 30 μg/dL were iron deficient.[3] In our study, only 11.6% of children with lead poisoning (blood lead concentration ≥ 10 μg/dL) had evidence of iron deficiency. It is noteworthy that in the study by Yip and colleagues, children were screened for lead poisoning on the basis of erythrocyte protoporphyrin concentration, which, as previously mentioned, increases with iron deficiency. Yip and colleagues' results may therefore have been influenced by a selection bias caused by the effect of iron deficiency on erythrocyte protoporphyrin concentration.

We are unaware of any previous studies showing, on the basis of data drawn from children screened for whole-blood lead concentrations, that laboratory evidence of iron deficiency is associated with low-level lead poisoning. Hammad et al., studying 299 inner-city children, showed an association between historical dietary iron intake and blood lead concentration but could not find an association between laboratory measures of iron deficiency and blood lead concentration.[16] Wolf et al., in a study of 184 Costa Rican children, also failed to find a relationship between iron deficiency and blood lead.[17] The failure of these 2 studies to detect an association between lead poisoning and laboratory measures of iron deficiency may have been due to a smaller sample size than that used in our study and therefore to lower statistical power.

The association of iron deficiency with low-level lead poisoning raises questions about the nature of the relationship between these 2 conditions. Whether the association is causal cannot be determined from our data. Because MCV, RDW, hemoglobin, and blood lead were measured simultaneously in the children in our study, inferences cannot be made about a temporal relationship among these factors. Both iron deficiency and lead poisoning occur more frequently in groups of lower than of middle or upper socioeconomic status, and their relationship may therefore be due to common environmental risk factors. Pica, for example, may be a risk factor for both iron deficiency and lead poisoning.

Nevertheless, there are data suggesting that iron deficiency predisposes to lead poisoning and that the relationship between the former and the latter is causal. Several studies have shown that iron-deficient animals absorb a greater percentage of ingested lead than do iron-replete animals and that iron deficiency increases lead retention[18,19]; Barton et al. suggested that the effects of iron deficiency on lead absorption are mediated through a common absorptive receptor.[19] These studies suggest that iron deficiency predisposes to lead poisoning. If iron and lead do bind competitively to the same absorptive receptor, the converse may also be true, with lead poisoning predisposing to iron deficiency.

The association of iron deficiency with low-level lead poisoning raises several issues of importance to public health. In our study, 1.1% of the children screened had both iron deficiency and lead poisoning. If this figure represents the concurrent incidence of these 2 conditions among inner-city children in the United States, thousands of US children have concurrent lead poisoning and iron deficiency. The consequences of this combination on neurodevelopmental outcome may be devastating, since both conditions have been shown to decrease attainment on scales of childhood development.[5,20,21] Because the worldwide prevalence of both iron deficiency and lead poisoning also remains quite high, the combined effect of the 2 conditions may

TABLE 2—Blood Lead Concentration in Relation to Selected Risk Factors

Variable (mean ± SD)	<5 μg/dL (<0.24 μmol/L)	5–9 μg/dL (0.24–0.43 μmol/L)	≥10 μg/dL (≥0.48 μmol/L)
Age, y*	1.9 ± 1.0	2.1 ± 1.0	2.2 ± 0.9
Hemoglobin (g/dL)	11.4 ± 0.9	11.5 ± 0.8	11.5 ± 0.9
MCV, fL**	76.3 ± 4.8	75.6 ± 5.3	74.9 ± 5.9
RDW	14.1 ± 1.3	14.2 ± 1.2	14.2 ± 1.2
Insurance status, n (%)***			
MassHealth	1204 (53.7)	814 (36.3)	225 (10.0)
Self-pay	286 (58.0)	165 (33.4)	42 (8.5)
Private insurance	548 (60.0)	290 (31.7)	76 (8.3)
Iron status, n (%)****			
Iron replete	1869 (56.8)	1119 (34.0)	301 (9.2)
Iron deficient	169 (46.8)	150 (41.6)	42 (11.6)

Note. Iron deficiency was defined as an MCV < 70 and RDW > 14.5 for children younger than 2 years and an MCV < 73 and RDW > 14.5 for children 2 years or older. MCV = mean corpuscular volume; RDW = red blood cell distribution width; MassHealth = Medicaid.
*P = .0001 by ANOVA for age and increasing blood lead concentration.
**P = .0001 by ANOVA for MCV and increasing blood lead concentration.
***P = .019 by χ^2 analysis for insurance status and increasing blood lead concentration.
****P = .001 by χ^2 analysis for iron deficiency and increasing blood lead concentration.

TABLE 3—Logistic Regression Modeling of the Association Between Iron Deficiency and Blood Lead Concentration

Independent Variable	Adjusted OR (95% CI) for Indicated Blood Lead Concentration ≥5 μg/dL	≥10 μg/dL
Iron deficiency	1.63 (1.29–2.04)*	1.44 (1.004–2.05)*
Age	1.28 (1.19–1.36)*	1.16 (1.03–1.29)*
Hemoglobin	1.09 (1.009–1.19)*	1.14 (0.99–1.31)
Insurance status		
MassHealth[a]	1.28 (1.09–1.51)*	1.24 (0.94–1.63)
Self-pay[b]	1.11 (0.88–1.39)	1.03 (0.69–1.53)

Note. Iron deficiency was defined as an MCV < 70 and RDW > 14.5 for children younger than 2 years, and an MCV < 73 and RDW > 14.5 for children 2 years or older. OR = odds ratio; CI = confidence interval; MH = Medicaid.
[a]Dichotomized as MassHealth vs private insurance.
[b]Dichotomized as self-pay vs private insurance.
*P < .05.

be profound on a global scale and especially in developing countries.[21]

Primary prevention of lead poisoning, such as by removing lead from the environment, is the major public health priority in providing protection to children at risk. However, the prevalence of lead is such that significant reductions in environmental exposure to it are not immediately feasible. Therefore, secondary preventive measures, such as selective dietary interventions to reduce the absorption of lead, should be simultaneously pursued. In this regard, dietary iron supplementation may limit lead absorption not only in iron-deficient children but also in those who are iron replete or only marginally iron deficient. This supplementation should be tailored to the individual child's nutritional status to prevent toxicity from excess dietary iron. Graziano et al. demonstrated an association between maternal iron deficiency and cord-blood lead concentration and suggested that iron supplements may be particularly useful in preventing lead absorption among pregnant women.[8]

There are limitations to our study. MCV and RDW are not direct measures of iron status and may not identify all children with iron deficiency. However, the American Academy of Pediatrics definition of iron deficiency used in our study is widely used clinically to diagnose this condition. Future studies with other markers of iron status, such as serum ferritin, are needed to verify our findings. A further limitation to our study was our inability to detect a dose–response relationship between iron deficiency and blood lead concentration. Because we could not quantify the lead doses of our subjects, we could not determine whether iron-deficient children had higher blood lead levels than did iron-replete children for a given dose of lead. Although one might expect a greater odds ratio for the association of iron deficiency with increasing blood lead levels of greater than 10 μg/dL, we may not have had adequate statistical power to detect this effect, since only 42 of the 3650 children in our study population were both iron deficient and lead poisoned.

Using a cross-sectional analysis of screening data in an urban, outpatient, primary care clinic, we found that iron deficiency as measured by red cell indices is associated with increased blood lead concentration. Further study of combined lead poisoning and iron deficiency is needed to better facilitate their prevention and treatment. On the basis of previous studies suggesting that iron deficiency increases lead absorption, such further study should include the investigation of dietary iron supplementation as a secondary measure for preventing lead poisoning. □

Contributors

R. O. Wright and H. Hu conducted the statistical analysis. R. J. Wright and M. W. Shannon assisted with statistical analyses. All 4 authors contributed to writing, revising, and evaluating the paper, and all approve the final version.

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