Interaction of Iron Deficiency and Lead and the Hematologic Findings in Children With Severe Lead Poisoning

Margaret Clark, MD, MPH, Joyce Royal, MD, and Ruth Seeler, MD

From the Division of Ambulatory Pediatrics and the Division of Pediatric Hematology, Cook County Children's Hospital, Chicago

ABSTRACT. Microcytic anemia, long considered an effect of lead poisoning, may in fact result from coexisting iron deficiency. In this study, how RBC size, hemoglobin, and zinc protoporphyrin vary as a function of iron status in a group of children with high lead levels was examined. Charts of all children (N = 51) admitted to Cook County Hospital for treatment of lead poisoning in 1981 to 1983 were reviewed for data on age, blood lead level, hemoglobin concentration, MCV, transferrin saturation and zinc protoporphyrin level. The mean lead level was 86 μg/dL and the range was 63 to 190 μg/dL. Children with transferrin saturation values less than 7% had a mean MCV of 56 μL, hemoglobin of 8.9 g/dL, and zinc protoporphyrin of 693 μg/dL; for those with saturations of 7% to 16%, the values were 61 μL, 10.1 g/dL, and 581 μg/dL, respectively; the children with saturations greater than 16% had normal mean MCVs and hemoglobin concentrations (74 μL and 11.4 g/dL) and a mean zinc protoporphyrin value of 240 μg/dL ($P < .0005$). Multiple linear regression was used to correct for effect of age, and transferrin saturation remained the most important predictor of MCV, hemoglobin, and zinc protoporphyrin levels; the addition of lead did not improve the models. Results of this study suggest that iron deficiency is strongly associated with some of the observed toxicities of lead. Also, lead poisoning can exist without producing microcytosis or anemia, and zinc protoporphyrin concentration may not be a sensitive indicator of lead level in the absence of iron deficiency. *Pediatrics* 1988;81:247–254; *lead, iron deficiency, anemia, microcytosis, zinc protoporphyrin.*

Despite recent advances demonstrating the toxicity of even low levels of lead exposure,[1] pediatricians in inner city areas are still encountering many children with significant chronic lead levels.[2,3] Many investigators have described the prevalence of microcytic anemia among children with lead poisoning,[4–8] and it is considered a hallmark of severe lead poisoning. However, iron deficiency, an undisputed cause of microcytic anemia, is also prevalent among such children.[9–12] This raises the question of whether the microcytic anemia in children with lead excess is the result of lead toxicity alone, the result of coexisting iron deficiency, or a result of interaction between the two.

In this study we evaluated how RBC size, hemoglobin concentration, zinc protoporphyrin levels, and the frequency of symptoms, vary as a function of iron status in a group of children with excessive lead levels.

MATERIALS AND METHODS

This study was approved by the Investigational Review Board of Cook County Hospital. The study population consisted of all children admitted to the hospital for inpatient treatment of lead poisoning from 1981 to 1983. At the time of the study, children were referred for inpatient chelation from the pediatric outpatient clinics of the hospital or the Chicago Board of Health if they had a blood lead level of 70 μg/dL or greater. Of 105 children identified from the admission logs, charts were located for 88; six patients were excluded because they were found after chart review not to have lead poisoning; seven other patients were excluded from the analysis because the child had an underlying condition that was likely to have an independent effect on hemoglobin level and/or RBC size. Therefore, data are presented for the 75 eligible patients.

All available data for the following study variables were extracted by retrospective chart re-

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Reprint requests to (M.C.) Department of Pediatrics, Suny Health Science Center at Brooklyn, Box 49, 450 Clarkson Ave, Brooklyn, NY 11203.

view: age, venous blood lead level, transferrin saturation, RBC count, MCV, hemoglobin concentration, zinc protoporphyrin level, and symptoms. Blood lead concentrations were determined either at the hospital[13] or at the Chicago Board of Health[14] using atomic absorption spectrophotometry after extraction. RBC count, hemoglobin levels, and MCV were measured by Coulter counter. Iron studies were done by standard colorimetric methods. Zinc protoporphyrin determinations were done on whole blood using an ESA hematofluorimeter; the majority were done by the Chicago Board of Health which is a reference laboratory for the Centers for Disease Control.

The highest of the prechelation blood lead values was used. No attempt was made to account for previous outpatient chelation therapy. For children with multiple inpatient courses, only the first hospitalization was used. Hemoglobin electrophoresis was done only if the routine sickle cell prep was positive.

A child was classified as symptomatic if any examiner recorded a history of abdominal pain, anorexia, vomiting, constipation, irritability, increased sleeping time, loss of milestones, seizures, or ataxia, according to the guidelines supplied by the *Pediatric Housestaff Manual* (Department of Pediatrics, Cook County Hospital, 1978, p 102). If the child had an intercurrent medical problem that could produce similar symptoms, the case was coded as "unknown." A determination regarding symptoms could be made in 62 children; 34 (59%) of them had prodromal symptoms of lead poisoning, although no child had encephalopathy. No attempt was made to categorize children according to the presence or absence of developmental delay.

Among those patients who had complete evaluations, the cases were stratified according to transferrin saturation, using the age-specific criteria of Koerper and Dallman.[16] The iron-deficient group was defined by a transferrin saturation of less than 7%, the marginal group had a saturation of 7% to 16%, and the adequate or replete group had a saturation greater than 16%. Anemia was defined as a hemoglobin value of less than 11.0 g/dL; microcytosis was defined as an MCV less than the third percentile for age, according to the standards of Dallman and Siimes.[17]

Intergroup differences in categorical variables were compared using the χ^2 test. Intergroup differences in continuous variables were compared using Student's t test; multiple linear regression was used to adjust for the effect of confounding variables. All analyses were carried out using the SAS computer package.

RESULTS

As a group, the 75 children had the classically described microcytic anemia of lead poisoning (Table 1), with a mean MCV of 66 μL, which is well below the third percentile for any age, and a mean hemoglobin value of 10.6 g/dL. As a group, they also had an elevated RBC count of 5.05 × 10^6/μL,[18] and a marginal transferrin saturation of 15.5%.

There were 51 children for whom there was complete data for iron status. These children had mean blood lead levels and ages comparable to the group as a whole; however, they had significantly lower hemoglobin and MCV values and much higher zinc protoporphyrin values than the 24 children from whom no iron studies were obtained (Table 2). This suggests an ascertainment bias on the part of the physicians in obtaining additional laboratory evaluation in the more anemic youngsters.

When these 51 children were classified according to iron status (deficient, marginal, adequate), a dramatic dose-response relationship emerged between iron deficiency and the three outcome variables, MCV, hemoglobin concentration, and zinc protoporphyrin value (Table 3). Although the children with adequate iron values were older than those with deficient and marginal iron status, there were no differences in mean lead values among the three groups. Mean MCV and hemoglobin value both increases steadily with increasing percentage of saturation, from a low of 56 μL and 8.9 g/dL, respectively, in the deficient group, to normal values, 74 μL and 11.4 g/dL, in the adequate iron group. Zinc protoporphyrin was determined for 37 of the 51 children with known iron status. Mean zinc protoporphyrin had a strong inverse relationship with transferrin saturation: the means were more than 500 μg/dL in the deficient and marginal groups but only 240 μg/dL in the group with adequate iron.

The prevalence of microcytosis and anemia and the occurrence of symptoms according to iron status are given Table 4. To assure enough subjects in each category, in this analysis the children with deficient and marginal iron were combined and compared with those with adequate iron values. The prevalence of microcytosis is strongly correlated with inadequate iron status, with an odds ratio of 43.5, $P = .0001$. A similar, although less dramatic, relation existed between anemia and inadequate iron status (odds ratio 12.5, $P = .001$) and the occurrence of symptoms (odds ratio 4.1, $P = .03$).

The association between iron adequacy and MCV, hemoglobin value, and zinc protoporphyrin

TABLE 1. Study Variables

Variables	No. of Children	Mean ± SD	Range
Age (mo)	75	29.1 ± 12.75	10–68
Lead (μg/dL)	75	85.1 ± 19.80	63–190
MCV (μL)	75	66.1 ± 10.65	42–84
Hgb (g/dL)	74	10.6 ± 1.6	6.6–13.7
RBC (No. × 10^6)	61	5.05 ± 0.56	4.02–6.32
Transferrin saturation (%)	51	15.5 ± 9.23	2.4–40.6
Zinc protoporphyrin (μg/dL)	57	433.5 ± 140.9	64–1,335

TABLE 2. Comparison of Study Variables in Patients With Known and Unknown Iron Status*

Variable	Patients With Iron Status Known		Patients With Iron Status Unknown		*P* Value
	Mean	No. of Patients	Mean	No. of Patients	
Age (mo)	29.8	51	27.7	24	.5
Lead (μg/dL)	86.3	51	84.5	24	.8
MCV (μL)	64.2	51	70.0	24	.04
Hemoglobin (g/dL)	10.2	51	11.5	23	.001
RBC (No. × 10^6)	5.06	41	5.01	20	.7
Zinc protoporphyrin (μg/dL)	515.0	37	281.1	20	.01

TABLE 3. Study Variables Compared by Iron Status

Variable	Iron Status			*P* Value*
	Deficient (n = 17)	Marginal (n = 14)	Adequate (n = 20)	
Age (mo)	25	28	35	<.05
Lead (μg/dL)	87	85	86	NS
MCV (μL)	56	61	74	<.0005
Hemoglobin (g/dL)	8.9	10.1	11.4	<.0005
Zinc protoporphyrin (μg/dL)	693 (n = 12)	581 (n = 14)	240 (n = 11)	<.005†

* Comparison by *t* test between each group.
† $P < .005$ for comparison between deficient and marginal; $P < .0005$ for comparisions between deficient/adequate and marginal/adequate.

TABLE 4. Prevalence of Microcytosis, Anemia, and Symptoms According to Iron Status*

	Iron Status		Odds Ratio	*P* Value
	Deficient or Marginal	Adequate		
Microtytosis	29/31 (93)	5/20 (25)	43.5	.0001
Anemia	27/31 (87)	7/20 (35)	12.5	.001
Symptoms	20/28 (71)	6/16 (37)	4.1	.03

* Numbers in parentheses are percentages

TABLE 5. Regression Model for Mean Corpuscular Volume*

Model	Variable						R^2
	Age		Transferrin Saturation		Lead		
	Bi	*P* Value	Bi	*P* Value	Bi	*P* Value	
Age + transferrin saturation	0.38	.000	0.61	.0001			.51
Age + lead	0.38	.0001			−0.11	.05	.24
Age + transferrin saturation + lead	0.38	.0005	0.61	.0001	−0.02	.85	.51

* Models take the form: MCV = B_0 + B_1 age + B_2 transferrin saturation + B_3 lead.

TABLE 6. Regression Model of Hemoglobin*

Model	Variable						R^2
	Age		Transferrin Saturation		Lead		
	Bi	*P* Value	Bi	*P* Value	Bi	*P* Value	
Age + transferrin saturation	0.03	.03	0.09	.0001			.41
Age + lead	−0.04	.01			−.01	.5	.13
Age + transferrin saturation + lead	0.04	.03	0.09	.0002	−.01	.6	.41

* Models take the form: hemoglobin = B_0 + B_1 age + B_2 transferrin saturation + B_3 lead.

TABLE 7. Regression Model of Zinc Protoporphyrin*

Model	Variable						R^2
	Age		Transferrin Saturation		Lead		
	Bi	*P* Value	Bi	*P* Value	Bi	*P* Value	
Age + transferrin saturation	−5.9	.12	−14.4	.01			.27
Age + lead	−3.5	.28			5.53	.01	.13
Age + transferrin saturation + lead	−5.9	.12	−12.3	.03	5.37	.30	.31

* Models take the form: zinc protoporphyrin = B_0 + B_1 age + B_2 transferrin saturation + B_3 lead.

concentration remains significant after using multiple regression to adjust for age (Tables 5 to 7). The best models for both MCV and hemoglobin include only age and saturation. There was no significant association between blood lead concentration and either MCV or hemoglobin concentration after adjusting for age and percentage of saturation.

Zinc protoporphyrin levels were not dependent on age. However, age was retained in the models because it was clearly an important possible confounder. Transferrin saturation and blood lead levels were both modest predictors of zinc protoporphyrin values, although transferrin saturation accounted for more variability than blood lead levels. The best model only predicted 30% of the variability in zinc protoporphyrin values. When log zinc protoporphyrin was used as the outcome variable, the trend persisted: saturation alone predicted 34% of the variability, whereas lead values alone still only predicted 10%.

No evidence of interaction between lead and transferrin saturation was detected for any of the three outcome variables, MCV, hemoglobin concentration, or zinc protoporphyrin value.

DISCUSSION

Both excessive lead levels and iron deficiency have an effect on hemoglobin concentration and RBC size. However, concurrent iron deficiency appears to be the most potent factor producing the microcytic anemia that is so prevalent among children with severe lead poisoning. The majority of lead-poisoned children who had adequate iron stores had normal hemoglobin concentrations and

MCV values, whereas those with inadequate iron status had microcytic anemia.

This set of findings is consistent with those of other investigators.[19,20] For instance, during the 1960s several investigators[21] found that the anemia in lead poisoned children was corrected by oral iron, before or after chelation therapy. More recently, Cohen et al[22] studied a group of children with class III and IV lead levels. Once children with iron deficiency or hemoglobinopathies were excluded, both microcytosis and anemia were rare.

Almost a third of the patients in the present study did not have iron studies performed. As presented in Table 2, these children were more likely to have normal hematologic findings and a lower zinc protoporphyrin value. Because the results of a CBC and zinc protoporphyrin level obtained as an outpatient were frequently known at the time of admission, this suggests an ascertainment bias: the housestaff appears to have been more likely to forego obtaining iron studies if the child's CBC was normal. It is important to assess how such a bias would affect the results of this study. If anything, it tends to reinforce the conclusion that a significant excessive lead concentration can exist without microcytic anemia or extreme elevations of zinc protoporphyrin values.

There is only one other study in which the hematologic indices in children with both lead poisoning and iron deficiency are described. In 1958 Watson et al[23] reported ten children whose lead levels and transferrin saturations were comparable to the iron deficient subjects in this study. These children were also anemic (mean hemoglobin 7.4 g/dL) and had severe microcytosis (MCV 57 μL). In both studies, the degree of microcytosis for a given reduction in hemoglobin appears to be greater than that reported for "pure" iron defiency anemia.[23–27] The RBC count in the lead-poisoned children was normal in the study by Watson et al and it was elevated in ours. This contrasts to the usual finding of a depressed RBC count in pure iron deficiency[23–27] and suggests a synergism between lead and iron deficiency in the pathogenesis of the microcytosis that does not produce an invariable reduction in RBC number. We did not see any statistical evidence of such an interaction in the regression analysis probably because we did not have any children with "pure" iron deficiency.

Because the children with lower iron stores are younger than the iron-replete children, it might be argued that the observed trends in hemoglobin concentration and MCV reflect nothing more than the normal developmental increments in these parameters.[17] However, the dependence of hemoglobin and MCV on iron status persisted even after multiple regression analysis was used to adjust for the effect of age.

The zinc protoporphyrin level was clearly elevated in every case, but most dramatically with a co-existent iron deficiency, in which case the mean zinc protoporphyrin concentration was more than 500 μg/dL of whole blood. By contrast, Piomelli et al[28] report that a free erythrocyte protoporphyrin to hemoglobin ratio of 17.5 μg/g of hemoglobin (equivalent to approximately 200 μg/dL of whole blood) is the upper limit for pure iron deficiency. As with the effects on MCV and hemoglobin, this suggests a synergism between iron deficiency and lead poisoning. Among the children studied during the second Health and Nutrition Examination Survey, Yip[12] found an interaction effect between low transferrin saturation and blood lead elevations in the range of approximately 25 μg/dL. Hryhorczuk et al[29] also found such a synergism in adults with occupational lead exposures. We were unable to demonstrate an interaction effect statistically in this study, probably because we did not have a group of children with "pure" iron deficiency, ie, with low transferrin saturations and blood lead values less than 25 μg/dL.

Zinc protoporphyrin level showed almost no statistical dependence on lead level in the regression model that included transferrin saturation and only slight dependence in the model in which lead was the only variable. This is in contrast to most other studies,[30–32] which report an exponential relationship between blood lead levels and erythrocyte protoporphyrin levels. There are several possible explanations for this discrepancy. First, the classic studies of Piomelli et al[28,30–32] demonstrating an exponential relationship between blood lead and erythrocyte protoporphyrin levels measure free erythrocyte protoporphyrin after extraction by ether.

Zinc protoporphyrin, on the other hand, is measured in whole blood, which makes it especially useful for field screening programs.[33] A recent study by Kaul et al[33] of children screened in New York City demonstrated that zinc protoporphyrin behaves differently from free erythrocyte protoporphyrin. Looking at paired specimens, they found that values of zinc protoporphyrin tended to be lower than those of free erythrocyte protoporphyrin, and the dependence on blood lead was less ($r = .37$ for zinc protoporphyrin v $r = .53$ for free erythrocyte protoporphyrin.

Second, many workers have suggested that there is a time lag between acute lead exposure and the accumulation of erythrocyte protopor-

phyrin, especially zinc protoporphyrin.[34] Three of our patients suggest that they were screened before the zinc protoporphyrin reached peak values; they all had zinc protoporphyrin values less than 150 μg/dL yet had blood lead levels of at least 70 μg/dL on initial screening that increased further by the time the children were admitted.

Third, although Piomelli et al[32] reported no evidence of a plateau effect at high levels of blood lead, in none of the published reports does the range extend beyond 100 μg/dL. The population in this study had blood lead levels in a generally higher range, which was truncated at the bottom. Because there is considerable scatter in the erythrocyte protoporphyrin values at the upper blood lead range,[30] the correlation between erythrocyte protoporphyrin and blood lead levels previously described may not be detectable without data points from the lower blood lead range.

Finally, it should also be noted that the studies of Piomelli et al[30–32] correlating lead and free erythrocyte protoporphyrin did not directly assess iron status. The second Health and Nutrition Examination Survey data reveal that 25% of children with lead toxicity also have a transferrin saturation less than 12%[12]; hence, iron deficiency is a major confounder in the relationship between lead and free erythrocyte protoporphyrin.

Because of its technical simplicity, zinc protoporphyrin is widely used as a first step screening test for lead poisoning. The results of this, as well as a previous study,[33] raise questions about how well it performs. All of the children in this study would have been detected on screening as needing confirmatory venous blood lead levels. There were four patients who had two blood lead levels greater than 70 μg/dL, and zinc protoporphyrin levels in the 50- to 109-μL range (placing them in a category of the 1978 Centers for Disease Control screening classification described as "combination of results not generally seen in practice"[35]). Zinc protoporphyrin as a screening tool would not have identified them as being at urgent risk of lead poisoning, with blood levels high enough to potentially produce encephalopathy. (It may be important to note that three of these four children were shown to have adequate iron stores.) This anomaly supports the warning stated by Kaul et al[33] about the possible lack of sensitivity of the zinc protoporphyrin as a screening test—a concern that is amplified now that our goal is to detect children with pretoxic lead levels.[1] Indeed, even when free erythrocyte protoporphyrin is used children with levels in the range we are now targeting for intervention may not be detected. In the study by Piomelli et al[31] only 50% of children with blood lead levels of 40 to 49 μg/dL were found to have free erythrocyte protoporphyrin values of 250 μg/dL of RBC, which is considerably higher than the free erythrocyte protoporphyrin value of 35 μg/dL of whole blood now recommended as the upper limit of normal.

Certain limitations of the data used in this analysis deserve comment. First, blood lead levels were used to estimate total body lead content, even though blood lead level reflects several dynamic processes. However, without measures of urinary lead excreted after administration of ethylenediaminetetraacetic acid, it was not possible to use the ratio of chelatable lead to obtain a closer approximation of internal dose of lead.[37] When a child had two blood lead values, we chose to use the higher of the two, believing it reflected better the dose of lead ingested, before distribution and elimination processes reduced the blood fraction. This meant pooling data from two laboratories, which would tend to weaken an association between blood lead and other variables. However, because of the time lag between screening and admission, the magnitude of the changes in blood lead values we observed were often much greater than the magnitude attributable to laboratory error.[13] In fact, most studies in children correlating protoporphyrins to lead level have used a single blood lead value.[31–33]

With few exceptions, the zinc protoporphyrin measurements were done by the Chicago Board of Health. However, some of the determinations were done elsewhere, including in the field. Because this was a retrospective study, the data to which we had access were collected for clinical use rather than for research purposes. The lack of complete uniformity of method would tend to obscure an association between zinc protoporphyrin and either blood lead or transferrin saturation.

Third, transferrin saturation is no longer the method of choice for detecting iron deficiency. Instead, many recent studies conclude that the "gold standard" for detecting iron deficiency is the demonstration of an increase in hemoglobin concentration after a therapeutic trial of iron, as summarized by Dallman.[38] Unfortunately, such an operational definition does not permit quantitation of the degree of iron deficiency for the purposes of regression analysis. The bias from using transferrin saturation, rather than a more sensitive indicator such as ferritin, would be toward underestimating the occurrence of iron deficiency.[38]

Finally, because there was no standardized instrument for recording the presence of symptoms, the correlation between iron deficiency and symp-

tom occurrence is open to question. The results are reported, however, because they do suggest an interesting trend: the iron-deficient children were more likely to have symptoms attributable to lead poisoning than were those with adequate iron. Hence, four easily assessed indicators of lead toxicity, namely, symptom occurrence, anemia, microcytosis, and elevated zinc protoporphyrin levels, are all strongly associated with coexistent iron deficiency. Nutritional studies reviewed by Mahaffey[39] have already demonstrated that iron-deficient subjects are likely to absorb a larger portion of an ingested dose of lead. Hence, coexistent iron deficiency truly puts children at double jeopardy from undue lead exposure.

Although the emphasis in the management of lead poisoning has been changing steadily since the 1960s, the new 1985 recommendations represent a dramatic change[1]: The goal now is to detect and treat children with low levels of lead in their blood before they experience any overt clinical toxicity. To this end, the target for screening has been reduced to a blood lead level of 25 μg/dL and an erthyrocyte protoporphyrin level of 35 μg/dL. Tragically, in many parts of the country, the reality is still far from these ideals. A recent report from Newark, NJ,[2] details how the economic recession has not only produced a deterioration in the rental housing stock, allowing increased lead exposure, but has also fueled cutbacks in budgets for screening programs: the net result in Newark was an increase in the hospital admission rate for lead poisoning between 1976 and 1980, after an earlier decline. These economic forces are surely applicable in other urban areas as well. Thus it remains important to determine how lead affects diverse body systems, to better evaluate the large numbers of children who are still being exposed to lead.

Work is in progress to extend this study prospectively to children with lead levels less than 70 μg/dL, measuring zinc protoporphyrin, free erythrocyte protoporphyrin, and transferrin saturation simultaneously, and including a group of children with "pure" iron deficiency.

In summary, contrary to one of the precepts of pediatric teaching, a child can have a significant blood lead excess without either microcytosis or anemia.

This is especially likely to happen if the child has adequate iron stores; therefore, an elevated blood level should never be discounted because of the absence of anemia or microcytosis. There are situations in which knowing the zinc protoporphyrin blood level alone may not allow detection of a child who is in urgent need of intervention for lead exposure. This occurred in three children in this study who had adequate iron levels. All children with chronic lead levels need to be assessed for iron deficiency, because coexistent iron deficiency may enhance the child's risk. Further work is needed to determine how erythrocyte protoporphyrin, and specifically zinc protoporphyrin, functions as a screening test for both lead poisoning and iron deficiency in the context of the new Centers for Disease Control screening guidelines.

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TEEN STATS

Everyday more than 3000 teen-age girls become pregnant, and 1300 babies are born to adolescents. Five hundred teen-agers have abortions, 26 girls age 13 and 14 have their first child, and 13 others who are 16 have their second child. Over the course of a year, one of every 10 teen-age girls becomes pregnant.

Submitted by Student

From Brozan N: Success in preventing teen-age pregnancy. *The New York Times*, March 14, 1987.