Elevated Lead Levels in Children With Nonorganic Failure to Thrive

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ABSTRACT. Every child with failure to thrive has at least one organic medical disease: malnutrition. It is well documented that lead and other heavy metals are absorbed more readily in the presence of both malnutrition and iron deficiency anemia. Malnutrition and lead exposure tend to be found in the same population groups. Furthermore, lead poisoning is correlated with many of the identical intellectual and behavioral deficits demonstrated in children suffering from nonorganic failure to thrive. Because of these facts, whole blood lead levels were determined for 45 children with nonorganic failure to thrive and 45 age-, race-, and socioeconomically matched comparison subjects. Children with failure to thrive had a lead level of 22.67 ± 10.29 (μg/dL (mean ± SD); for control children, it was 14.33 ± 5.42 ($P < .001$). Children with failure to thrive were more frequently anemic ($P < .0001$), a possible lead effect, and had higher free erythrocyte protoporphyrin levels. Children with failure to thrive were developmentally delayed on the Denver Developmental Screening Test (unblinded observation) with high failure rates in both language ($P < .001$) and gross motor skills ($P < .02$). Although failure on the Denver Developmental Screening Test within the failure to thrive group was not linearly correlated with lead level, any such effects may have been masked by the effects of malnutrition and failure to thrive per se. A number of authors have suggested that lead levels formerly thought to be inconsequential are clinically toxic. Lead levels in the 15- to 20-μg/dL range interfere with heme synthetase activity and the synthesis of CNS neurotransmitters. Increased lead levels, malnutrition, and iron deficiency are all potentially etiologic in the developmental disabilities ascribed to failure to thrive. Pediatricians should screen all at-risk children with failure to thrive for elevations in lead levels, developmental delay, and iron deficiency. Given that malnutrition per se is synonymous with failure to thrive and may result in increased lead absorption, pediatricians should immediately take steps to ensure adequate caloric intake in children with failure to thrive. The treatment of such biomedical problems as elevated lead levels, malnutrition, and iron deficiency may ameliorate some of the behavioral, cognitive, and interactive deficits observed in nonorganic failure to thrive. Parenting difficulties observed in families with children who fail to thrive may be exacerbated by the child. *Pediatrics* 1986;78:891–895; *lead, temperament, development, failure to thrive.*

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LEAD POISONING: BACKGROUND DATA

Lead poisoning has been and continues to be recognized as a serious health problem among children from all geographic and socioeconomic groups, especially those in urban areas. According to statistics from the National Health and Nutrition Examination Survey,[1] 4% of children 6 months to 5 years of age had elevated blood lead levels in 1976 to 1980. The persons at greatest risk for lead poisoning are children between the ages of 1 and 5 years, especially those children living in pre-World War II housing, children with a history of abnormal oral behaviors such as pica, and children who are inadequately supervised.[1]

Another survey conducted in the United States between 1976 and 1980 documented that 3.9% of US children younger than 5 years of age had blood levels of 30 μg/dL or greater.[2] These authors extrapolated from their data that 675,000 children in the United States had elevated blood lead levels. Of white children, 2% had elevated lead levels, and of black children, 12.2% had these levels. Among the poorest strata of the black population, inner city residents with incomes of less than $6,000 per annum, 18.6% of the children had elevated lead levels. Now that the Centers for Disease Control has decreased its definition of elevated lead levels from 30 to 25 μg/dL, the percentage of children suffering from lead toxicity appears to be even greater.[3] It is now documented that lead levels as low as 15 to 20 μg/dL interfere with heme synthetase activity and also with monamine oxidase activity.[3] These enzymes regulate the rate-limiting steps in hemoglobin synthesis and the rate of production of serotonin, a CNS neurotransmitter. Further studies have demonstrated a synergistic effect on hemoglobin levels between lead toxicity and iron deficiency in children.[4] Many authors have shown the deleterious effect on child temperament, maternal child interaction, intellectual development, and achievement of children with elevated lead levels.[5-7] Deficiencies in iron, calcium, and phosphorous seem directly linked to elevated lead levels.[8,9] Decreased dietary calcium and iron intake actually promote lead's intestinal absorption.[10,11]

FAILURE TO THRIVE BACKGROUND

"Nonorganic" failure to thrive is a growth disorder of infancy and early childhood afflicting as many as 10% of the rural outpatient population.[12] It also accounts for 1% of all pediatric hospitalizations[13] and 80% of infants with failure to thrive are younger than 18 months of age. Although there are discrepancies in the diagnostic criteria for failure to thrive, the term is typically used to describe infants and young children whose weights are persistently below the third percentile for age on appropriate standardized growth charts.[13]

The etiology of failure to thrive is traditionally dichotomized into organic and nonorganic categories. Nonorganic failure to thrive is defined as a failure of growth without diagnosable organic disease, whereas organic failure to thrive is a growth symptom for virtually all serious pediatric illness.[14-16] Recently, a number of authors have questioned the adequacy of such a dichotomous view of failure to thrive, suggesting instead that in approximately 25% of cases the etiology was mixed and could not be ascribed to purely organic or nonorganic causes alone.[17]

Further studies[11] suggest that three etiologic categories are minimally necessary to adequately describe causation in failure to thrive: organic, nonorganic, and mixed (both organic and inorganic). Sameroff and Chandler[18] have suggested that there exist a continuum of reproductive (organic) and caretaking (nonorganic) causualty in diseases such as failure to thrive. Whether or not children with failure to thrive have organic, nonorganic, or mixed etiology, all children who fail to thrive have suffered an organic insult: malnutrition. All children with failure to thrive have either not taken, not been offered, or not retained adequate calories.

Such undernutrition has significant effects on later growth, cognition, and behavior. Malnutrition in and of itself presents in myriad forms classically manifesting in irritability, high distractability, anorexia, and both cognitive and motoric developmental delay.[14] Such developmental and temperamental aberrations may well produce aberrant behavioral/interactive patterns between parents and infants, while exacerbating failure to thrive.[14] These aberrant behavioral patterns seem virtually identical with those described for lead poisoning.

It is well documented in animal studies that malnutrition results in increased absorption of heavy metal.[11,19] Malnourished children are also at risk for lead poisoning on the epidemiologic grounds of age, race, and socieconomic status. Furthermore, lead poisoning is correlated with many of the identical intellectual and behavioral deficits demonstrated in children suffering from malnutrition. Because of these observations, and the fact that both lead poisoning and malnutrition are strongly associated with poverty,[20] we designed the following study to determine whether children with failure to thrive in our clinic had elevated blood lead levels.

MATERIALS AND METHODS

Whole blood lead levels were determined for 45 children with nonorganic failure to thrive and 45 age-, race-, and income-matched comparison subjects. All children diagnosed as having nonorganic failure to thrive had complete medical and nutritional histories done. A feeding observation and initial laboratory screen including determinations of hemoglobin, hematocrit, lead, free erythrocyte protoporphyrin, ESR, electrolytes, urinalysis, and urine culture were done. Other laboratory tests were performed as indicated, eg, pH probe if vomiting was a concern. All children with nonorganic failure to thrive had weights and heights for age less than the fifth percentile on the National Center for Health Statistics growth grids. Cases were derived from an inner city pediatric primary care clinic based in a tertiary care pediatric teaching hospital. Children with failure to thrive were entered into the study during a 18-month period. Twenty-eight children were referred to the author by other providers in the primary care clinic. The other 17 patients were children from the author's primary care practice. Thus, 100% of all children with failure to thrive seen by the author were enrolled in the study. In addition to the previously mentioned laboratory studies, the Denver Developmental Screening Test was administered to all children. (The administration of this test was unblinded, except that the author was unaware of the lead levels of the patients because this was done at the time of the first clinic visit before any laboratory test results were available.) Of the 45 children with failure to thrive, 30 were black, nine were white, and six were Hispanic. Comparison subjects were chosen consecutively by one-to-one matching of clinic patients for age ±3 months, race, sex, and socioeconomic status.

RESULTS

Undernourished children did not differ from control children in age, race, or socioeconomic status (Table 1). Their weights were significantly different: children with failure to thrive had a mean weight of 8.1 kg (18 lb) and control children 11 kg (24.5 lb). Of the entire sample, 18% lived in public housing (ten children with failure to thrive, six control children). More families with children who failed to thrive described their homes as having peeling paint somewhere in the house (ten failure to thrive *v* six comparison families) (nonsignificant *P* value). Homes were owned by 16% of the families (nonsignificant *P* value). Two of the five children with lead values greater than 40 μg/dL had peeling paint at home.

The major difference observed between the two groups were their hematologic values (Table 2). Children with failure to thrive had a blood lead level of 22.67 ± 10.29 μg/dL (mean ± SD) and control children 14.33 ± 5.42 μg/dL. This difference was highly significant by Student's *t* test ($P < .003$). The standard deviation was approximately twice as large in the failure to thrive group *v* the comparison group. This is accounted for by the fact that there was marked skew in the lead levels measured for children with failure to thrive, with five of the 45 children (approximately 11%) having lead levels greater than 40 μg/dL. Because of this skew in the data, to confirm the findings, lead levels for the two groups were also compared using the Wilcoxon sign rank test, a nonparametric statistical test ($P < .0011$). The markedly different, more gaussian distribution of lead levels in the comparison group is shown in the Figure.

To determine whether the differences in lead levels between the two groups were clinicially significant using the Centers for Disease Control standards,[3] the Fisher exact test with a cut-off point of 25 μg/dL yielded $P = .01$. For a lead level greater than 30 μg/dL, the difference between children with failure to thrive and control children gave $P < .001$.

The significant difference in the prevalence of

TABLE 1. Characteristics of Study Groups

Characteristic	Failure to Thrive Group	Control Group
Mean age (mo)	18.5	18.0
Mean wt (kg [lb])	8.1 (18.5)	11 (24.5)
Mean income ($)	12,105	12,592
Mean lead level ± SD (μg/dL)	22.67 ± 10.29*	14.33 ± 5.42*

* $P < .003$; 95% confidence interval, 6.2, 10.5.

TABLE 2. Hematologic Values for Study Groups*

	Failure to Thrive Group	Control Group
Hemoglobin (g/dL)	10.22 ± 0.95†	11.5 ± 0.82†
Free erythrocyte protoporphyrin (μg/dL)	65 ± 25	34 ± 15

* Results are means ± SD.
† $P < .0001$; 95% confidence interval, −1.38, −1.16.

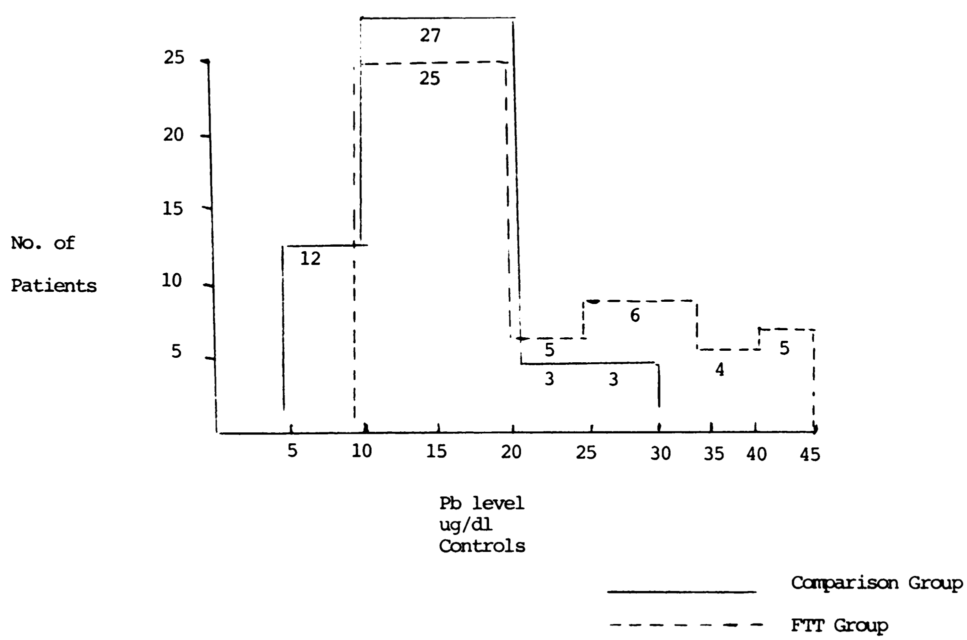

Figure. Lead level distribution in children with failure to thrive (FTT) and control children.

anemia in children with failure to thrive *v* comparison children is shown in Table 2.

There was a significant increase in failure rates for children with failure to thrive *v* control children on the Denver Developmental Screening Test in the area of language (Table 3). The *P* value for significance of the gross motor function screening was <.02. Children with failure to thrive did not differ significantly in terms of pica from control children. Pica is defined as placing nonfood objects in the mouth after 18 months of age.[21] Only ten children in each group were older than 18 months of age, however. Of the children with failure to thrive with lead levels greater than 40 μg/dL, all were older than 12 months of age. Two of the five children with failure to thrive with elevated lead levels had pica. Of the five children with lead levels greater than 40 μg/dL, three failed the Denver Developmental Screening Test language screen and two failed the gross motor screen.

DISCUSSION

Obviously, there are limitations to the present study: no group of children with failure to thrive from a nonurban environment is included and it is likely that such children would not have elevated lead levels. Also, no serum ferritin levels were obtained to be certain that the anemia described in the failure to thrive group was indeed the result of iron deficiency, which is known to cause developmental dysfunction. In addition, a surprisingly low incidence of lead poisoning in the control population was found, even though the majority of children sampled were welfare dependent, poor, and, frequently, members of minority groups known to be at high risk for lead poisoning. Indeed, the comparison children had a lower incidence of elevated lead levels than the general patient population of our clinic. Lead poisoning in inner city Boston is such a prevalent problem that all children in our clinic are screened for elevated lead levels every 6 months between the ages of 1 and 5 years. A further limitation of our study was the fact that the author was not blinded as to failure to thrive *v* comparison status of the children and thus may have inadvertently prejudiced the results of the Denver Developmental Screening Test. This, however, is unlikely because the author adhered to the recommended uniform presentation and scoring of the test.[22] These data are of interest given that the Denver Developmental Screening Test has recently been shown to be superior to the Stanford-Binet test in predicting later cognitive functioning.[23] Also, the use of the Denver Developmental Screening Test probably results in underreporting of failure rate in both groups given its "screening" character which only allows identification of children who should be retested for probable developmental delay.

TABLE 3. Denver Developmental Screening Test Failure Rates

Area Tested	Failure to Thrive Group	Control Group	*P* Value*
Personal/social	2/45	1/45	NS
Fine motor	0/45	1/45	NS
Gross motor	5/45	0/45	<.02
Language	9/45	0/45	<.002

* Fisher exact test.

In spite of the limitations, these data add further weight to the argument that many children with nonorganic failure to thrive may have concomitant medical illness. A number of authors have recently suggested that lead levels formerly thought to be inconsequential are indeed clinically toxic. Lead levels in the 15- to 20-μg/dL range interfere with both heme synthetase activity and the synthesis of CNS neurotransmitters such as serotonin.[13] Elevated lead levels, malnutrition, and iron deficiency anemia have all been described as potentially etiologic in developmental disabilities identical with those ascribed to failure to thrive per se, including anorexia, temperamental-behavioral aberrations, and delays in cognitive and motor functioning. In our study, 16% of all children diagnosed as having no organic medical cause for their growth failure had lead levels that might require chelation therapy depending on clinical presentation. Sameroff and Chandler's hypothesis of a continuum of organic and caretaking casualty in diseases such as failure to thrive may well be correct.

No significant correlation exists between either increased lead levels, or anemia, and failure on the Denver Developmental Screening Test. This may simply reflect the developmental devastation associated with failure to thrive per se. Such delays are associated with malnutrition alone and may simply mask the more subtle developmental changes associated with lead level elevation and anemia. Furthermore, the Denver Developmental Screening Test may be inadequately sensitive to diagnose these more subtle developmental problems.

It is not clear from this study whether malnourished children do indeed absorb a greater amount of ingested lead than control children. It is known, however, that iron-deficient patients absorb a higher percentage of ingested lead than comparison subjects.[19] Perhaps, the parenting difficulties described in these families result in the child having more unsupervised time, thus allowing a higher intake of lead-containing paint or soil. Although the reason for the increased lead levels observed remains largely unknown, it seems clear from these data that the parenting difficulties observed in some of the families with undernourished children may be exacerbated by the child him- or herself.

Pediatricians should screen all at-risk, undernourished children for lead level elevation and iron deficiency. The treatment of such readily remediable, biomedical problems may rapidily ameliorate or at least clarify the etiology of some of the behavioral and interactive deficits observed in children with nonorganic failure to thrive. These data should further suggest to the clinicians dealing with failure to thrive that the definition of the at-risk child be viewed more broadly. Behavioral, socioeconomic, and biomedical factors are once again shown to reinforce each other. A number of authors have shown that children living in high socioeconomic status seem to be protected from the effects of organic medical insults.[24-27] The ways in which high socioeconomic status protect children may be more varied than suspected. The effect of high or low socioeconomic status may effect children not only via social and psychologic vectors but also by altering organic, biochemical, or physiologic processes in ways often not even considered in the past.

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