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IMPROVING BEHAVIOR OF LEAD-EXPOSED CHILDREN: MICRONUTRIENT SUPPLEMENTATION, CHELATION, OR PREVENTION

In this issue of *The Journal*, Kordas et al[1] report no improvement in parent or teacher rating of behavior after a 6-month course of iron and/or zinc supplementation in 7-year-old Mexican children with elevated blood lead concentrations. The study was conducted in the city of Torreon, Mexico, in which a metal foundry is located close to the city center. The children enrolled were from public elementary schools near the foundry, and had a mean blood lead concentration of 11.5 μg/dL. (For comparison, the current mean in the Unites States is about 2 μg/dL.) These children also had a high prevalence of iron deficiency (22%) or zinc deficiency (29%). In this double-blind randomized controlled trial, it was hypothesized that iron and/or zinc supplementation would improve behavioral ratings through a direct effect of iron and/or zinc on behavior or through reduced blood lead concentrations. But it was found that the supplementation produced no marked change in blood lead concentrations after 6 months. This report corroborated a previous report that clinical treatment aimed at lowering blood lead concentration does not improve cognitive and behavioral scores of lead-exposed children. In the Treatment of Lead-Exposed Children (TLC) clinical trial, succimer chelation effectively reduced blood lead concentrations for up to 9 or 10 months in 2-year-olds with mean blood lead concentration of 26 μg/dL, but it did not improve IQ and neurobehavior test scores at 3 or 5 years after treatment.[2,3]

One reason for the negative results reported in these studies may be that the children were exposed to relatively high levels of environmental lead (such as the metal foundry in the Kordas et al Mexican study and inner-city housing in the TLC study) during the early postnatal period, when the brain might be most sensitive to lead, and that such damage could not be reversed by later treatment. Although some studies do support the hypothesis that period of infancy and toddlerhood is a critical window of susceptibility for lead-induced cognitive defects, others have found lifetime exposure or concurrent blood lead concentration to be more strongly associated with IQ at the school-age period.[4,5] Close examination of the lead–IQ association in the TLC study found that blood lead concentration measured at school age was more predictive of IQ measured at school age than was peak blood lead measured at about age 2 years.[6] The association between lead and behavior in the TLC study is currently under investigation. We speculate that continuous childhood exposure may be more detrimental to a child's neuropsychological function than exposure in the early postnatal period only.

TLC Treatment of Lead-Exposed Children

Another possible explanation for the findings of Kordas et al is that the dosage of iron and/or zinc was not sufficient concentration or that the supplementation was not given for a sufficiently long period to affect blood lead. Although the dosage of iron and/or zinc used in the Kordas et al study was higher than the U.S. recommended daily allowance (10 mg/day iron and 5 mg/day zinc for children age 4 to 8 years[7]), the study subjects had a relatively high prevalence of iron or zinc deficiency. Supplementation at these levels may not reverse iron or zinc deficiency very rapidly, and its effect on blood lead concentration in such a short period may not be evident as was assumed, especially if the exposure to lead does not cease. In TLC clinical trial, up to 3 rounds (of 26 days each) of succimer treatment produced a significant reduction in blood lead concentrations for 9 to 10 months but had no long-term affect on concentrations measured at the 3- and 5-year follow-up, when the cognitive and neurobehavioral tests were given. It is not clear how long an intervention is required to produce a sufficient reduction in blood lead concentrations to affect test scores, and clinical trials to determine this would be long, costly, and difficult.

Even though the Kordas et al study found no improvement in mean scores of behavioral tests after the treatment, it did find that children who received zinc (zinc only or zinc and iron) were less likely to have clinically significant teacher reports of oppositional behavior after treatment.[1] At the same time, the percentage of children with clinically significant scores in teacher-rated hyperactivity, cognitive problems, and attention deficit hyperactivity disorder and any of the four parent-rated problems did not change. The finding for oppositional behavior may be a chance finding, significant because of the multiple comparisons involved in the study, and should not be overinterpreted. However,

See related article, p 632.

Reprint requests: Walter J. Rogan, MD, Epidemiology Branch, NIEHS, MD A3-05, PO Box 12233, Research Triangle Park, NC 27709. E-mail: rogan@niehs.nih.gov.
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even though iron and/or zinc do not appear to improve behavior, children with dietary deficiencies should generally receive supplementation.

Although the median blood lead concentration in US children has declined remarkably over the past 2 decades,[8] data in 1998 showed that 25% of US homes with 1 or more children under age 6 years still had significant amounts of lead-contaminated deteriorated paint, dust, or adjacent bare soil.[9] Lead is a neurotoxicant, and commonly seen elevated blood lead elevations are associated with cognitive impairment, with no threshold observed.[10-12] The association between lead and non-IQ behavioral outcomes independent of IQ effect is receiving increasing attention, with emphasis on aggressive, inattentive, hyperactive, antisocial, and delinquent behaviors.[4] In the study by Kordas et al, baseline blood lead concentration was also associated with teacher rating of behavior scores and the prevalence of subscale scores within the clinically significant range.

Current data on lead exposure and its effects on cognitive function and behavior suggest that lead poisoning in children remains a public health concern in the United States.[13] Because attempts at improving cognitive and behavioral ratings of lead-exposed children with micronutrient or chelation therapy have been unsuccessful to date, the importance of primary prevention is highlighted. In addition, programs aimed at reducing lead exposure should not focus exclusively on 1- to 2-year-old children, because increasing evidence suggests that prolonged exposure into the school-age period may do more harm than was once thought. The cost and benefits of lead abatement in old houses have been estimated, and removing lead paint is believed to be a cost-effective measure.[9,14]

Aimin Chen, MD, PhD
Epidemiology Branch
National Institute of Environmental Health Sciences
National Institutes of Health
Department of Health and Human Services
Research Triangle Park, NC 27709

Walter J. Rogan, MD
Epidemiology Branch
National Institute of Environmental Health Sciences
National Institutes of Health
Department of Health and Human Services
Research Triangle Park, NC 27709

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SORTING OUT THE CAUSES OF ALPS

See related article, p 691.

Autoimmune lymphoproliferative syndrome (ALPS) is a prototypic disorder of abnormal lymphocyte homeostasis. Defective programmed cell death of lymphocytes (apoptosis) through the Fas (CD95) pathway occupies a central role in the pathogenesis of ALPS. Homeostasis through apoptosis is important to remain within the limited containment capacity of the lymphoid compartment to eliminate autoreactive lymphocytes and to prevent malignant transformation of lymphocytes.[1] Consequently, the main manifestations of ALPS are lymphoproliferation, reflected in

ALPS Autoimmune lymphoproliferative syndrome

Reprint requests: Jack J. H Bleesing, MD, PhD, Cincinnati Children's Hospital Medical Center, Division of Hematology/Oncology, 3333 Burnet Ave/ MLC 7015, Cincinnati, OH 45229. E-mail: jack.bleesing@cchmc.org.
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