ELSEVIER

Toxicology 97 (1995) 11–17

TOXICOLOGY

Adverse health effects of lead at low exposure levels: trends in the management of childhood lead poisoning

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Received 15 February 1994; accepted 20 February 1994

Abstract

An extensive database has provided a direct link between low-level lead exposure during early development and deficits in neurobehavioral-cognitive performance evident late in childhood through adolescence. These consistent studies have demonstrated the presence of a constellation of neurotoxic and other adverse effects of lead at blood lead (BPb) levels at least as low as 10 μg/dl). Federal agencies and advisory groups have redefined childhood lead poisoning as a BPb level of 10 μg/dl. Before discussing some of these studies in greater detail, the pervasiveness of this entirely preventable disease today in millions of American children must be recognized.

Keywords: Lead; Young children; Neurobehavioral-cognitive performance

1. Introduction

During the past 6–7 years, an extensive database has been published providing a direct link between low level lead (Pb) exposure in young children and deficits in neurobehavioral-cognitive performance manifested later in childhood through adolescence (Fulton et al., 1987; Hansen et al., 1989; Hatzakis et al., 1989; Hawk et al., 1986; Lansdown et al., 1986; Lyngbye et al., 1990; Schroeder et al., 1985; Winneke et al., 1990; Yule et al., 1981; Needleman et al., 1990; McMichael et al., 1988; Bellinger et al., 1987; 1991; 1992; Dietrich et al., 1989; Schwartz et al., 1993; Needleman and Gatsonis, 1990; Baghurst et al., 1992). These highly consistent results, with few exceptions (Ernhart et al., 1987), have demonstrated a constellation of adverse neurotoxic and biochemical effects of Pb at blood lead (BPb) values at least as low as 10 μg/dl. Thus, federal agencies and other advisory groups have redefined childhood lead poisoning as a BPb level ≥10 μg/dl (CDC, 1991a; CDC, 1991b; US EPA, 1990a,b; ATSDR, 1988; US EPA, 1986; US HUD, 1990; NAS, 1993; AAP, 1993). These agencies and advisory groups arrived at this definition of childhood lead poisoning through consensus of informed lead experts and through preparation of scientific documents assessed by the peer review system

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SSDI 0300-483X(94)02963-U

(CDC, 1991a; CDC, 1991b; US EPA, 1990a,b; ATSDR, 1988; US EPA, 1986; US HUD, 1990; NAS, 1993; AAP, 1993).

Pb is a multimedia toxicant that provides toxic risks even when source specific exposures appear relatively modest (ATSDR, 1988). All sources of Pb are integrated systemically into critical target organs; and the margin of safety for children is remarkably narrow. Today, as in previous decades, lead-based paint is the major source of exposure leading to poisoning. It is estimated that ~75% of pre-1980 housing contains hazardous quantities of leaded paint (CDC, 1991a); the current extent inventory of leaded paint in US housing is estimated at 3 million tons (NAS, 1993).

About 14 million children ≤7 years of age are at high risk because they live in pre-1959 housing that contains the highest concentrations of leaded paint (ATSDR, 1988; US HUD, 1990). According to the US Department of Housing and Urban Development (US HUD, 1990), an estimated 20 million houses contain peeling lead-based paint; nearly 4 million of these homes are occupied by families with children ≤7 years of age. White children 0.5–5 years of age constitute the largest group (>11 million) of children at risk in the United States. Based upon 1984 estimates, ~4.5 million white children today are expected to have a BPb value ≥10 μg/dl (ATSDR, 1988; Crocetti et al., 1989; Crocetti, 1992; Rosen, 1992) (Table 1). As shown in the table, the largest number of white children with BPb levels ≥10 μg/dl are from the highest social strata, although the prevalence rate is higher among the other two groups (Table 1). Overall, ~40% of white children are estimated to have BPb concentrations >10 μg/dl. In minority populations, the total number of affected children is less compared with white children, whereas the prevalence rates are considerably higher. These data indicate that virtually all young children are at risk of lead poisoning; and these data form the foundation for the Centers for Disease Control's recommendation for universal BPb testing in young American children (CDC, 1991a).

2. Neurobehavioral and cognitive deficits secondary to lead at low exposure levels

The results of several well designed cross-sectional and retrospective cohort studies support

Table 1
Estimated prevalence rates and numbers of urban white children (aged 0.5–5 years) with blood lead (BPb) levels >10 μg/dl by family income[a]

Annual Family Income	Data
≥$15 000	
No. of children	7 643 900
No. with BPb >10 μg/dl	2 473 700
Calculated prevalence	32.4%
$6000–14 999	
No. of children	2 666 300
No. with BPb >10 μg/dl	1 322 900
Calculated prevalence	50%
<$6,000	
No. of children	1 039 600
No. with BPb >10 μg/dl	709 300
Calculated prevalence	68.2%
Total	
No. of children	11 349 800
No. with BPb >10 μg/dl	4 515 900
Calculated prevalence	39.8%

[a]From: ATSDR, 1988; Crocetti et al., 1989; Crocetti, 1992; Rosen, 1992.

the conclusion that decreases in children's cognitive abilities occur at BPb levels ≥ 10 μg/dl (Fulton et al., 1987; Hansen et al., 1989; Hatzakis et al., 1989; Hawk et al., 1986; Lansdown et al.; 1986; Lyngbye et al., 1990; Schroeder et al., 1985; Winneke et al., 1990; Yule et al., 1981); and no threshold for lead-IQ relationships can be delineated from these studies (CDC, 1991a). The associations observed in these studies (Fulton et al., 1987; Hansen et al., 1989; Hatzakis et al., 1989; Hawk et al., 1986; Landsdown et al., 1986; Lyngbye et al., 1990; Schroeder et al., 1985; Winneke et al., 1990; Yule et al., 1981) remain significant when multiple covariates are accounted for. Based upon cross-sectional and retrospective studies, these IQ deficits have been found to be irreversible (Needleman et al., 1990; CDC, 1991a; NAS, 1993).

In the past 5–8 years, cross-sectional studies have been supplemented by longitudinally designed prospective studies in which investigators gain information about the timing and extent of exposure, as well as many other covariates (McMichael et al., 1988; Bellinger et al., 1987, 1991, 1992; Dietrich et al., 1989; Schwartz et al., 1993; Baghurst et al., 1992). Additional strengths of prospective studies (Mushak et al., 1989) include the use of standardized methods for assessing exposure and various outcomes, employment of statistical methods to control for multiple covariates and potential confounders, enrollment of cohorts of sufficient size to yield enough power to detect subtle effects, and assessment of the full scope of childhood development longitudinally from birth to several years of age. Furthermore, through the use of consistently applied outcome measures, prospective studies can be compared directly. These prospective studies have further changed the way in which public health and regulatory federal agencies and advisory groups approach childhood lead poisoning (CDC, 1991a; CDC, 1991b; US EPA, 1990a,b; ATSDR, 1988; US EPA, 1986; US HUD, 1990; NAS, 1993; AAP, 1993); results of these studies unequivocally confirm evidence linking low levels of lead exposure (10 μg/dl) to neurobehavioral-cognitive impairments. The Cincinnati (Ohio) study (Dietrich et al., 1989) found effects of prenatal lead exposure on Mental Developmental Index scores that amounted to an eight-point deficit for each 10 μg/dl increase in BPb levels. The study in Port Pirie, Australia (McMichael et al., 1988) evaluated children up to 4 years of age, and related integrated BPb levels to the McCarthy Scales of Children's Abilities. Blood lead levels were inversely related to cognitive scores in children at 4 years of ago when the BPb value was 30 μg/dl, compared with children who had BPb levels ≤ 10 μg/dl. The difference between these two groups was 7.2 points on cognitive scores. These adverse findings persisted through 7 years of age (Baghurst et al., 1992).

Perhaps the most unique prospective study, now in its tenth year, is being carried out in Boston (Massachusetts) (Bellinger et al., 1987, 1991, 1992). The Boston cohort is composed of advantaged middle- and upper-class children. Few children have access to the social and economic advantages in the Boston cohort. These advantaged children could be expected to be at the least risk for having lead-induced cognitive deficits. The effect of lead on cognitive functioning of these children at extremely low exposure levels has been demonstrated. Small increases in BPb levels above a mean value of 6.3 μg/dl at 24 months of age were associated with a decrease of 5.9 points on the General Cognitive Index of the McCarthy Scales at 57 months of age, when the mean BPb level was 6.5 μg/dl. The General Cognitive Index decreased by −3 points for each natural log unit increase in BPb level at 24 months. This cohort was characterized by maternal IQ scores of 124 ± 16 (mean ± SD), Mental Development Index scores on the Bayley Scales of 116 ± 16 at 24 months, and General Cognitive Index of 115.5 ± 14.5 at 57 months. Further analyses between BPb levels and General Cognitive Index fail to reveal a threshold down to BPb levels of ≤ 2.0 μg/dl (Schwartz, 1993).

The Boston cohort has now been assessed at 10 years of age, when the mean BPb level was 2.9 μg/dl (Bellinger et al., 1992). Slight elevations in BPb levels (~5 μg/dl) at 2 years of age were associated at 10 years of age, without an apparent threshold, with significant impairments in intellectual and academic performance, assessed by the Wechsler Intelligence Scale for Children - Revised and the Kaufman Test for Educational Achieve-

ment. An increase in BPb levels slightly greater than 10 μg/dl at 24 months was associated with a 6.0 point decline in the full-scale IQ on the Wechsler Intelligence Scale for Children - Revised and an 8.9 point decrease on the Kaufman Test for Educational Achievement (Bellinger et al., 1992).

The link between low-level lead exposure during early development and later deficits in intellectual and academic performance is remarkably consistent; there is compelling consistency in effect size estimates in BPb-IQ-neurobehavioral outcomes. If large variations existed, this would suggest confounding by omitted variables or an omitted effect modifier (Schwartz, 1993). The weighted average effect size is a highly significant summary of the weight of these data from multiple studies. In this approach, individual studies are treated as data points in a larger 'meta-study.' This technique is known as meta-analysis. The usefulness of this technique is that it permits the investigator to combine the results of studies that differ in some respect, while examining the same research questions (Needleman and Gatsonis, 1990). Seven studies were so analyzed, and the effect-size estimates were quite similar and highly significant (Schwartz, 1993). Overall, these data indicated an average decrease of 0.25 IQ points for each 1.0 μg/dl increase in BPb levels. This inverse relationship between IQ and BPb levels continued below 10 μg/dl (Schwartz, 1993). Another meta-analysis of 13 such studies (Needleman and Gatsonis, 1990; Needleman, 1987), yielded a joint P value of <0.0001 for the negative correlation between blood lead values and IQ. Thus, the overall pattern strongly supports the conclusion that low-level lead exposure is related directly to neurobehavioral and cognitive deficits. These results of the prospective and cross-sectional studies and the meta-analyses indicate causality between remarkably low levels of lead exposure and neurobehavioral-cognitive-IQ deficits in young children.

The public health implications of a 4–6-point deficit on various tests of neurobehavioral and cognitive functioning may not be clinically devastating to an individual child. However, a downward shift of 4 points in the normal distribution of mental developmental indexes on the Bayley Scales or other neurobehavioral-cognitive outcome measures for a population of children would result in 50% more children scoring in the borderline range of 80 (Grant and Davis, 1989). Similarly, such a downward shift in neurobehavioral-cognitive-academic functioning would result in an absence of children who achieved superior scores (>125) (CDC, 1991a).

3. Trends in the management of childhood lead poisoning

Our group has been studying treatment outcomes in a longitudinal assessment of untreated lead poisoned children during the past 6 years (Fig. 1). If the BPb value at enrollment was 25–54 μg/dl and the erythrocyte protoporphyrin (EP) concentration in whole blood was ≥35 μg/dl, L-line X-ray fluorescence (LXRF) estimate of tibial bone Pb (Rosen et al., 1989, 1991; Rosen and Markowitz, 1993: Markowitz et al., 1993) was followed by a comprehensive neurobehavioral assessment (Ruff et al., 1993). One week later, each child underwent a $CaNa_2EDTA$ provocative test. If this test was positive, lead-poisoned children were admitted to the hospital for 5 days of $CaNa_2EDTA$ therapy at a daily dose of 1000 mg/m^2 given in 4 divided doses/day intravenously. During the 6-month period of study, if a child had

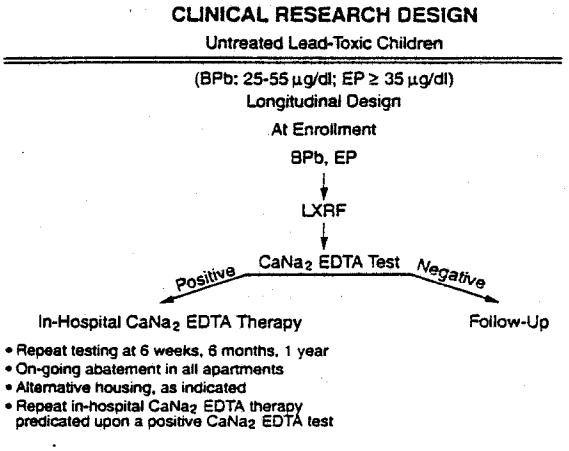

Fig. 1. Clinical research design (Ruff et al., 1993; Markowitz et al., 1993).

a positive provocative test, additional 5-day courses of $CaNa_2EDTA$ were administered. Abatement of lead paint hazards was achieved in most apartments by the time of initial hospital discharge. In ~20% of children, alternative housing was obtained with family or friends or via transition housing in a designated building at our Center (the Safe House) until housing repairs were completed. From the standpoint of medical and environmental interventions, management of these children is considered to be optimal.

4. Cognitive changes and declining BPb levels in moderately lead-poisoned children

The purpose of this study was to determine, under the most 'ideal' circumstances of medical and environmental intervention, whether chelation therapy and/or biochemical changes during a lead-lowering intervention was associated with changes in cognitive functioning of moderately lead-poisoned children. It was hypothesized that cognitive performance would improve as blood lead level declined over time (Ruff et al., 1993).

A total of 154 previously untreated children referred to our Center with blood lead levels in the range 25–54 μg/dl were enrolled. Ages were in the range 13–87 months. Enrolled children were treated with $CaNa_2EDTA$ if eligible and/or with orally administered iron supplement if iron deficient. For all children, housing inspections and abatement procedures were performed as necessary and completed in a timely manner, as indicated above. The main outcome measure was scores on the Bayley Mental Development Scale or Stanford-Binet Intelligence Scale (4th edition).

There was no effect of $CaNa_2EDTA$ treatment per se. In the short term (7 weeks), changes in blood lead levels were not related to changes in cognitive scores. In the long term (6 months), however, changes in performance were significantly related to changes in blood lead level, even after controlling for confounding variables. The standardized score increased 1 point for every decrease of 3 μg/dl in blood lead level.

The results of this study contribute to the understanding of the effects of moderate lead poisoning in young children and provide results that confirm and supplement those from a number of studies with different methods. These data are consistent with the presence of an association between cognitive changes and changes in lead levels. Further research into the cognitive effects of chelation treatment and other forms of intervention is clearly needed (Ruff et al., 1993).

Strictly controlled studies demonstrating the efficacy of $CaNa_2EDTA$ in inducing a sustained reduction in BPb level or lead-related toxicity have not been performed in children with moderate lead poisoning. This study assessed the relationship between $CaNa_2EDTA$ chelation and measures of lead burden and toxicity in children with moderate lead poisoning.

A group of 201 children with moderate lead poisoning was enrolled. Sequential changes in BPb concentrations, bone lead level as measured by Lα-X-ray fluorescence, and lead-induced toxicity as assessed by erythrocyte protoporphyrin levels were determined over a 7-week period (Fig. 1). From this group, children with a positive lead mobilization test received $CaNa_2EDTA$ chelation therapy. Children with negative $CaNa_2EDTA$ provocative tests were followed longitudinally with the same test battery as children with positive provocative tests (Markowitz et al., 1993).

Children with positive lead mobilization tests had on average higher initial BPb, bone lead, and erythrocyte protoporphyrin concentrations. The chelated children decreased ~4.7 μg/dl, 41 corrected net counts, and 24 μg/dl more than the unchelated children on BPb, bone lead, and erythrocyte protoporphyrin values, respectively. However, children with higher initial levels decreased the most, whereas children with lower initial levels showed the least decline, with or without treatment. When the initial values on the measures were controlled analytically, or when subgroups matched on initial levels were compared, there were no significant differences between the chelated and unchelated children (Markowitz et al., 1993).

The apparent effectiveness of $CaNa_2EDTA$ in reducing lead burden and toxicity is no longer observed when the pretreatment levels are considered. These findings suggest that sufficient doubt about $CaNa_2EDTA$ efficacy now exists to

warrant a randomized controlled trial of chelation therapy with $CaNa_2EDTA$ and Succimer (DMSA) in moderately lead-poisoned children. However, until such studies are performed, it would be premature to withhold chelation treatment on the basis of this study alone.

5. Conclusion

More than 20 years have elapsed since the Lead Paint Poisoning Prevention Act was passed, yet lead poisoning from leaded paint is the most common preventable disease today in the pediatric age group (ATSDR, 1988). The enormous societal/financial/human costs to this country have been extensively documented by the EPA (US EPA, 1990c) and Centers for Disease Control (CDC, 1991b). Yet, as of this writing, CDC's plan to eradicate childhood lead poisoning from leaded paint has not been implemented (CDC, 1991b). Childhood lead poisoning is a national disease of major dimensions that has a markedly negative effect on the 'competitiveness' of American Society. But a national response, which is central to eradicating this preventable disease, is not yet evident. Until a meaningful national program is instituted and focused on eradicating extant leaded paint in US housing, the full growth potential of hundreds of thousands of American children is likely to be irreversibly sacrificed.

Acknowledgements

Collaboration with Drs. K. Balbi, P. Bijur, M. Markowitz and H. Ruff is gratefully acknowledged.

Note added in proof

Since this manuscript was completed in 1993, the U.S. Department of Health and Human Services has completed a national blood lead survey carried out between 1988 to 1991. Although the total number of lead poisoned children has decreased to 8.9%, largely as a result of the decade-old phasedown in leaded gasoline, the health of about 4 million American children is adversely affected by lead poisoning. Children especially at high risk are minority, urban and from low income families (*JAMA* 1994; 272:277–283). In this category of children, one to five years of age, the prevalence of lead poisoning was 6.1% in white, 36.7% in African-American and 17% in Hispanic children.

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