Lead Level ≥5 μg/dL and Neurodevelopmental Outcomes of Preterm Infants at Five Years of Age

ASHLEY ADAMS, MD; MICHELLE L. ROGERS, PHD; ELISABETH C. McGOWAN, MD; RICHARD TUCKER, BA; BETTY R. VOHR, MD

ABSTRACT

INTRODUCTION: Prior studies have not examined blood lead levels (BLL) in the preterm population relative to their developmental and behavioral outcomes.

METHODS: Neonatal demographic and clinical characteristics and results on scales of intelligence, development, and behavior were compared between children born ≤32 weeks gestation (n=354) with detected lead levels in childhood of ≥5 μg/dL (n=37, 10%) and <5 μg/dL (n=317, 90%).

RESULTS: The 10% rate of BLL ≥5 μg/dL for this cohort was higher than rates previously reported for the general population, and was associated with low SES. Preterm infants with a lead level of ≥5 μg/dL were twice as likely to score in the borderline to clinical range for sleep problems on the Childhood Behavioral Checklist.

CONCLUSIONS: Robust screening and follow-up may protect against negative developmental outcomes in the setting of elevated lead levels. The association of higher lead levels with poor sleep supports continued lead screening efforts and appropriate support services for preterm children.

KEYWORDS: lead exposure, preterm infants, development, behavior

INTRODUCTION

Childhood lead exposure has been associated with cognitive, behavioral, and motor deficits throughout the life course.[1-7] Cognitive difficulties associated with lead exposure have included lower IQ, poorer information processing, and impaired attention.[5,6] Studies of the effects of lead exposure on motor development have found that exposure can cause impaired fine motor functioning, and that lead levels were inversely correlated with measures of bilateral coordination, upper limb speed, dexterity, and visuomotor functioning in young children.[5,8] Lead exposure has also been linked to a spectrum of behavioral problems including increased rates of depression, aggression, anti-social behavior and sleep problems, and may even play a mediating role within the relationship between social adversity and externalizing behaviors in children.[6]

In 2012, the Centers for Disease Control and Prevention (CDC) lowered the standard "level of concern" for lead exposure from ≥10 μg/dL to 5 μg/dL and recommended discontinuation of a designated "level of concern," as research has shown that there is no "safe" level of blood lead.[3,9] In May 2021, the CDC again updated the elevated blood lead reference value to 3.5 μg/dL. The CDC currently recommends that children with a blood lead level (BLL) ≥3.5 μg/dL be referred for follow-up, as per CDC guidance.[10] In Rhode Island, universal blood lead screening is required by law for all children by three years of age and it is recommended that all children from nine months to six years of age be screened at least once annually.[11]

Infants born prematurely are at increased risk for delayed cognitive and motor development as well as behavioral problems.[12-17] The period from 20 to 37 weeks gestation is one of rapid brain development; birth during this time alters the trajectory of development and can lead to lasting brain abnormalities.[15] Preterm infants are often delayed in crawling and walking, and experience impairment in fine and gross motor skills.[15,18] Studies of cognitive functioning have found that delays exist in infancy and early childhood[13,17] and can persist through school age.[12,14]

CDC data shows that from 2012–2018, the percent of children ages one-three years living in Rhode Island with BLL ≥5 μg/dL decreased from 6.5% to 2.9%.[10] Data are not available, however, on former preterm infants. Preterm infants with delayed onset of crawling and walking may be exposed to increased and/or a prolonged window of exposure to environmental lead sources. To date, no studies have examined rates of BLL in the preterm population relative to developmental and behavioral outcomes. A decision was made to analyze study groups by the cut-point of 5 μg/dL, consistent with the cut-point recommendation for the time period the samples were collected, and consistent with the majority of previous studies that use a cut-point for elevated blood lead level. Since multiple lead levels were reported for children with increasing age, the highest recorded lead level was used for analysis.

The study objectives therefore were to: 1) identify the rate of BLL ≥5 μg/dL in a defined cohort of children born preterm and 2) examine rates of cognitive delays, motor delays and behavior problems for children with BLL ≥5 μg/dL compared to <5 μg/dL at five years of age. It was hypothesized that

preterm children with a BLL ≥5 μg/dL would have higher rates of cognitive, motor and behavior problems at five years of age compared to children with a BLL <5 μg/dL.

METHODS

The study was approved by the Women & Infants Hospital (WIH) and the Rhode Island Department of Health Institutional Review Boards and informed consent was waived because of the retrospective study design. The cohort consisted of 354 infants <33 weeks gestation born 2005 to 2014 and seen in the follow-up clinic for a five-year visit between 2010 and 2019.

The study was conducted at WIH, which has a level 3–4 Neonatal Intensive Care Unit (NICU) and a Neonatal Follow-up Clinic. Maternal and infant demographic and clinical characteristics and morbidities are collected prospectively in conjunction with longitudinal follow-up data. Preterm infants are considered high risk for developmental challenges and are automatically referred to the Neonatal Follow-up Clinic. Initial study eligibility included birth weight ≤1250 grams and a gestation of 22 to <33 weeks.

The follow-up clinic provides longitudinal multidisciplinary assessments and clinical management of high-risk infants. Certified examiners perform comprehensive medical, neurologic and developmental assessments. Infants in the study cohort were born between 2005 and 2014 and cared for in the NICU and Follow-up Clinic.

ASSESSMENTS

Tests administered included the Wechsler Preschool and Primary Scale of Intelligence (WPPSI III and IV),[19,20] the Child Behavior Checklist (CBCL),[21] the Behavior Rating Inventory of Executive Function Preschool (BRIEF-P),[22] the Developmental Test of Visual Motor Integration (VMI),[23] and the Movement Assessment Battery for Children (ABC-2).[24] Two versions of the Wechsler were used since the test was updated in 2012 from the WPPSI III to the WPPSI IV. The WPPSI was designed to measure cognitive development for children age two-and-a-half to seven years of age. Both versions of the test have a mean and standard deviation of 100±15. The BRIEF-P is a parent self-report questionnaire that examines behavioral problems in preschoolers associated with difficulties with executive function. A score ≥65 is rated as potentially clinically elevated.

The Child Behavior Checklist (CBCL) is a widely-used standardized instrument designed to assess the social competencies and behavioral problems of children aged three to 18 years. Parents complete 100 questions regarding their child's performance in sports, classroom activities, chores, and the quality of relationships with friends and family. The CBCL provides T-scores (≥65 meets criteria for borderline clinical significance; ≥70 meets criteria for clinical significance) for internalizing behavior, externalizing behavior, and total behavior problems. The Visual Motor Integration (VMI) and Movement ABC-2 are assessments of fine motor and gross motor development, respectively.

Sample size: There were 354 preterm children (born to 321 mothers) with comprehensive neonatal and outcome data for whom BLLs were available to be linked from the Rhode Island KIDSNET database.

STATISTICAL ANALYSES

Descriptive analyses were used to compare social environment and clinical characteristics (infant sex, gestational age, neonatal health outcomes, maternal age, maternal insurance coverage, maternal primary language, etc.) and test scores of preterm children with a highest lead level of <5 μg/dL compared to ≥5 μg/dL. Group comparisons based on the BLL categories were made using bivariate analyses, with Fisher's exact test used for categorical variables and t-tests for linear variables. Multivariate regression models were explored to assess independent effects of lead.

RESULTS

Maternal and infant demographics and clinical characteristics compared across preterm group with highest lead level of <5 μg/dL vs. ≥5 μg/dL closest to the time of their 60-month exam are shown in **Table 1**. A total of 37 (10%) premature infants in our sample had a maximum lead level ≥5 μg/dL and 317 (90%) had a maximum lead level <5 μg/dL. Of the 37 infants with elevated BLLs, 65% (n=24) were initially tested with venous samples and 35% (n=13) were initially tested via capillary sample. Of the 13 infants with BLLs ≥5 μg/dL initially tested by capillary sample, n=6 were subsequently tested via venous sample per recommendations from the Rhode Island Department of Health Childhood Lead Poisoning Prevention Program[25]; n=2 were confirmed within three months by venous sample which remained ≥5 μg/dL, n=3 had a follow up venous sample obtained within a month that was <5 μg/dL, n=1 had a follow-up venous sample six months later that was <5 μg/dL, and n=7 did not have their level confirmed by venous sample. The two study groups had similar mean maternal age, maternal marital status, history of prenatal care, non-Hispanic White versus Black, Indigenous, and people of color (BIPOC) racial identity, and education level. However, the group with high lead levels ≥5 μg/dL were significantly more likely to have Medicaid insurance (p=0.01) and have mothers who were non-English speaking (p=0.03).

The two study groups also had similar neonatal demographic and clinical characteristics including gestational age, birthweight, sex, and singleton birth status. Infants

Table 1. Maternal and Infant Characteristics by Highest Lead Level*

	Highest Lead Level by Time of 60-month Exam		
MATERNAL CHARACTERISTICS			
M ± SD or N (%)	**<5 μg/dL (N=288, 89.7%)**	**≥5 μg/dL (N=33, 10.3%)**	**P value****
Maternal Age	30.4 ± 5.9	30.2 ± 6.3	0.82
Maternal Age < 20	8 (2.8)	0 (0.0)	1.00
Not Married	120 (42.4)	19 (57.6)	0.14
Had Prenatal Care	282 (97.9)	32 (97.0)	0.54
Medicaid Insurance	137 (48.1)	22 (68.8)	0.04
Non-Hispanic White	193 (67.3)	23 (69.7)	0.85
Some college	175 (71.1)	13 (52.0)	0.07
Non-English speaking	31 (10.8)	8 (24.2)	0.04
INFANT CHARACTERISTICS			
M ± SD or N (%)	**<5 μg/dL (N=317, 89.6%)**	**≥5 μg/dL (N=37, 10.4%)**	**P value****
Gestational age	27.6 ± 2.5	26.8 ± 2.2	0.07
Birth weight	1005.5 ± 348.7	957.9 ± 211.9	0.24
SGA, weight <10%	71 (22.4)	2 (5.4)	0.02
Male	148 (46.7)	21 (56.8)	0.30
Multiple	80 (25.4)	9 (24.3)	1.00
IVH 3-4 or PVL	21 (6.6)	0 (0.0)	0.15
BPD	87 (27.5)	7 (18.9)	0.33
ROP	134 (42.8)	17 (46.0)	0.73
NEC (proven)	15 (4.7)	3 (8.1)	0.42
Sepsis (early or late)	53 (16.7)	8 (21.6)	0.49
Days of oxygen	37.4 ± 43.6	33.3 ± 33.3	0.58
Days on ventilator	9.3 ± 17.0	7.9 ± 11.5	0.51
Days in NICU	79.0 ± 38.5	80.3 ± 27.3	0.79
Breast Milk at discharge	155 (53.8)	15 (46.9)	0.46
Cerebral Palsy at 2 years	21 (6.7)	1 (2.7)	0.67

*Highest lead level among all lead tests completed by time of 60-month exam.
**P values from Fisher's exact test or two sample t-test.

Table 2. WPPSI-III & WPPSI-IV Scores by Highest Lead Level*

	Highest Lead Level by Time of 60-month Exam		
M ± SD or N (%)	**<5 μg/dL (N=314)**	**≥5 μg/dL (N=37)**	**P value****
WPPSI-III & WPPSI-IV			
Full Scale IQ	89.3 ± 15.5	88.6 ± 19.0	0.79
Full Scale IQ <85	106 (33.9)	13 (35.1)	0.86
Full Scale IQ <70	34 (10.9)	5 (13.5)	0.58

*Highest lead level among all lead tests completed by time of 60-month exam.
**P values from Fisher's exact test or two sample t-test

with highest lead level ≥5 μg/dL were less likely to be born small for gestational age (birthweight <10%; p=0.01). The two groups also had similar rates of neonatal morbidities, rate of receiving breast milk at time of discharge from the NICU, and a diagnosis of cerebral palsy at two years of age (**Table 1**).

WPPSI-II and WPPSI-IV scores were statistically similar for the two groups of children based on highest lead level (**Table 2**). Mean Full Scale IQ (FSIQ) scores were 89.4 and 88.6 for children with lead level <5 μg/dL and ≥5 μg/dL, respectively. There were also no differences between the two groups on the WPPSI score cut-points or subscales (analyses not shown).

CBCL T-scores ≥65 (borderline to clinical range) were higher for preterm children with a lead level ≥5 μg/dL but did not achieve statistical significance with the exception of sleep problems (p=.04) (**Table 3**). With the exception of somatic complaints, all rates of CBCL measures in the clinical range (CBCL T-scores ≥65) were higher for children with a BLL ≥5 μg/dL, although none were statistically significant. In multivariate models adjusting for Medicaid insurance, non-English primary language of caregiver, and SGA status, there was no significant association between blood lead level and CBCL scores.

The percent of children with BRIEF-P T-scores ≥65 did not differ between study groups. The percent with T-scores ≥65 on the BRIEF-P (19) subscales ranged from 11–21% for infants with a highest lead level <5 μg/dL and between 11–23% for infants with a highest lead level ≥5 μg/dL (**Table 4**). Visual Motor Integration (VMI) and Movement ABC-2 scores did not differ between groups. (**Tables 5,6**).

All analyses were repeated using the lead level cutoff of 3.5 μg/dL in accordance with the most recent CDC guidelines for lead level screening. In this secondary analysis, all comparisons demonstrated differences in the same direction as detailed above, but no longer met statistical significance.

Table 3. CBCL-T Scores in Borderline (T score ≥65) and Clinical Range (T score ≥70) by Highest Lead Level*

	Highest Lead Level by Time of 60-month Exam					
CBCL scores	**Borderline Range (T score≥65)**			**Clinical Range (T score ≥70)**		
N (%)	**<5 µg/dL (N=307)**	**≥5 µg/dL (N=34)**	**P value****	**<5 µg/dL (N=307)**	**≥5 µg/dL (N=34)**	**P value****
Total Problem	38 (12.4)	6 (17.7)	0.42	21 (6.8)	4 (11.8)	0.29
External	25 (8.1)	5 (14.7)	0.20	15 (4.9)	3 (8.8)	0.41
Internal	45 (14.7)	5 (14.7)	1.00	24 (7.8)	3 (8.8)	0.74
Emotionally Reactive	50 (16.2)	4 (11.8)	0.63	20 (6.5)	3 (8.8)	0.49
Anxious/Depressed	33 (10.7)	4 (11.8)	0.77	18 (5.8)	3 (8.8)	0.45
Somatic complaints	56 (18.2)	6 (17.7)	1.00	30 (9.7)	3 (8.8)	1.00
Withdrawn	35 (11.4)	6 (17.7)	0.27	26 (8.4)	6 (17.7)	0.11
Sleep problems	32 (10.4)	8 (23.5)	0.04	18 (5.8)	5 (14.7)	0.06
Attention	50 (16.2)	8 (23.5)	0.33	38 (12.3)	6 (17.7)	0.42
Aggressive behavior	21 (6.8)	4 (11.8)	0.29	16 (5.2)	3 (8.8)	0.42

*Highest lead level among all lead tests completed by time of 60-month exam.
**P values from Fisher's exact test or two sample t-test

Table 4. BRIEF-P T-Scores (N (%) for scores ≥ 65) by Highest Lead Level*

	Highest Lead Level by Time of 60-month Exam		
N, (%)	**<5 µg/dL (N=303)**	**≥5 µg/dL (N=35)**	**P value****
Global Executive composite (GEC)	58 (19.1)	7 (20.0)	0.82
Inhibitory Self-Control Index (ISCI)	49 (16.1)	6 (17.1)	0.81
Initiate	42 (13.9)	5 (14.3)	1.00
Emergent Metacognition index (EMI)	65 (21.4)	7 (20.0)	1.00
Inhibition	50 (16.5)	7 (20.0)	0.63
Shift	40 (13.2)	4 (11.4)	1.00
Emotional control (EC)	36 (11.9)	4 (11.4)	1.00
Working memory (WM)	65 (21.4)	8 (22.9)	0.83
Plan/organize (PO)	55 (18.1)	6 (17.1)	1.00

*Highest lead level among all lead tests completed by time of 60-month exam.
**P values from Fisher's exact test or two sample t-test

Table 5. Visual Motor Integration(VMI) Scores by Highest Lead Level*

	Highest Lead Level by Time of 60-month Exam		
M ± SD or N(%)	**<5 µg/dL (N=317)**	**≥5 µg/dL (N=37)**	**P value****
VMI Standard Scores	90.8 ± 12.3	91.6 ± 12.4	0.70
VMI <85	73 (23.3)	9 (24.3)	0.84
VMI <70	8 (2.6)	2 (5.4)	0.28

*Highest lead level among all lead tests completed by time of 60-month exam.
**P values from Fisher's exact test or two sample t-test

DISCUSSION

It is well-established that lead exposure and elevated BLLs in childhood are associated with negative cognitive, motor, and behavioral outcomes. To date, our study is the first to investigate BLLs and associated developmental and behavioral outcomes in children born prematurely. Ninety percent of our sample of premature infants had a maximum detected BLL <5 µg/dL, likely a testament to current strong public health and screening measures given the history of elevated BLLs in Rhode Island.[25] The social environment factors in our sample associated with infants having BLL ≥5 µg/dL (Medicaid insurance and maternal primary language) are consistent with previously reported associations between lower socioeconomic status and lead exposure.[26] While our study did not establish causality, hypothesized mechanisms for how these demographic measures may lead to higher child lead exposure include factors related to poverty, exposure to older homes, and differences in access to childcare and medical care.[26] The 10% rate of BLL ≥5 µg/dL for this preterm cohort was higher than rates previously reported for the general population,[10,27] suggesting that former preterm infants, especially those of low socioeconomic status, are at increased risk for lead exposure.

Contrary to our hypotheses based on existing literature correlating lead exposure with neurodevelopmental risk, there were no significant differences between infant groups detected on most cognitive, behavioral, and motor outcome measures. This lack of significance may be due to limitations in the study methods including limited sample size. Future studies can aid in exploring these questions further.

Our study did identify a significant association between BLL ≥5 µg/dL and the CBCL domain of impaired infants' sleep. Prior studies also report a correlation between elevated blood lead levels in early childhood and sleep problems in adolescence.[7,28] Possible mechanisms for this correlation may be a neurotoxic effect of lead on brain structures involved

Table 6. Movement ABC-2 scores (≤15th %) and ≤5th %by Highest Lead Level at Time of 60-month exam

	MABC-2 scores ≤15th %			MABC-2 scores ≤5th %		
N (%)	<5 μg/dL (N=287)	≥5 μg/dL (N=34)	P value**	<5 μg/dL (N=287)	≥5 μg/dL (N=34)	P value**
Manual Dexterity	214 (74.6)	23 (67.7)	0.41	189 (65.9)	17 (50.0)	0.09
Aim & Catch	81 (28.1)	11 (33.3)	0.55	58 (20.1)	8 (24.2)	0.65
Balance	128 (44.8)	12 (37.5)	0.46	82 (28.7)	9 (28.1)	1.00
Total Score	182 (65.7)	15 (48.4)	0.07	149 (53.8)	11 (35.5)	0.06

*Highest lead level among all lead tests completed by time of 60-month exam.
**P values from Fisher's exact test or two sample t-test

in sleep, other cognitive and behavioral outcomes that impact on sleep, or an interaction of both. Future studies are needed to investigate these possible mechanisms.

Study limitations include a limited sample size of preterm infants with elevated BLLs. We did not perform statistical analyses using a correction factor for multiple comparisons due to the nature of our small sample size and limitation in power. Further study of the effects of lead in preterm infants with a larger sample size is needed to confirm our findings and explore moderating effects on developmental outcomes, such as age of detection of elevated blood lead level, participation in early intervention, and other demographic factors. Strengths include a study sample that was recruited from a well-resourced NICU follow-up clinic in which infants receive regular neuro-logic screening, developmental testing, and referral to Early Intervention, Women, Infants, and Children (WIC), and social work as needed. An additional strength is access to a well-coordinated statewide universal lead screening program for children nine months to five years of age. Access to these resources through the follow-up clinic may mitigate the increased risk that lead exposure has on early developmental outcomes.

CONCLUSIONS

Our findings support the importance of lead screening, regular developmental assessment, and access to childcare resources, especially for vulnerable infants born prematurely. We identified that former preterm infants with Medicaid insurance and mothers who are non-English speaking are at increased risk of elevated blood lead levels, which are associated with a doubling of the rate of sleep problems at age five. Future studies with larger sample sizes are needed to evaluate the associations of lead exposure with long-term academic, behavioral, and health outcomes in children and adolescents with a history of prematurity. These data could potentially facilitate both early identification and initiation of intervention, and establish the importance of protective factors.

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Authors

Ashley Adams, MD, Department of Psychiatry and Behavioral Sciences, Boston Children's Hospital, Boston, MA.

Michelle L. Rogers, PhD, Department of Behavioral and Social Sciences, Brown University School of Public Health, Providence, RI.

Elisabeth C. McGowan, MD, Department of Pediatrics, Division of Neonatal Medicine, Warren Alpert Medical School of Brown University, Women and Infants Hospital, Providence, RI.

Richard Tucker, BA, Department of Pediatrics, Women and Infants Hospital, Providence, RI.

Betty R. Vohr, MD, Department of Pediatrics, Division of Neonatal Medicine, Warren Alpert Medical School of Brown University, Women and Infants Hospital, Providence, RI.

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Correspondence

Ashley Adams, MD
Department of Psychiatry and Behavioral Sciences
Boston Children's Hospital
2 Brookline Place
Brookline, MA 02445
Ashley.adams@childrens.harvard.edu