Journal of Environmental and Occupational Science
www.jenvos.com
DOI: 10.5455/jeos.20151029110613

Original Research

Neurocognitive Status of Andean Children with Chronic Environmental Lead Exposure

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Received: September 25, 2015
Accepted: October 16, 2015
Published: December 18, 2015

ABSTRACT

Aim: Chronic lead (Pb) exposure has been associated with neurocognitive impairment in children and adults, including deficits in attention, intelligence, memory, executive functions and behavior. Pediatric Pb exposure results in poor performance on neurocognitive tests that may be irreversible. The aim of the present study was to assess the long-term neurocognitive status of children with a history of chronic and high environmental Pb exposure. **Methods:** Pb exposure over time was determined by measurements of blood Pb levels (PbB) at two different test periods. Raven Coloured Progressive Matrices (RCPM) and the Digit Span test of auditory memory/attention were used to measure neurocognitive functioning. The study group of 28 Ecuadorian Andean children ranged in age from 4.8 to 15 years. **Results:** The mean PbB level of the children at the time of the first RCPM test was 49.3 μg/dL (SD: 30.1; range: 4.4-119.1), and indicative of Pb poisoning. The mean PbB level at the time of the second RCPM test was 37.4 μg/dL (SD: 23.1; range: 5-94.3), and consistent with chronic Pb exposure. Although PbB levels declined in the study group between the two test periods, performance on the RCPM and Digit Span tests tended to become poorer over time, suggesting long-term adverse neurocognitive effects of chronic Pb exposure. **Conclusion:** The findings of this study on children with chronic Pb exposure showed poorer performance on measures of visual-spatial intelligence and auditory memory/attention over a period of several years, suggesting increasing adverse neurocognitive effects of chronic Pb exposure.

KEY WORDS: Neurocognitive, Neurotoxicology, Lead, Children, Andean, Environmental

INTRODUCTION

Neurodevelopmental disorders and neurocognitive impairment, including deficits in attention, intelligence, memory, executive function and behavior, are well-established adverse outcomes of lead (Pb) exposure in children, even at low blood lead (PbB) levels [1-3]. The toxicological effects of Pb on the developing brain have been demonstrated in a number of studies that have reported an association between adverse neurocognitive function and pediatric Pb exposure [4-7]. Early childhood Pb exposure also has been found to be associated with subsequent impaired learning and poor cognitive test performance in children, and neurocognitive deficits in adulthood [5,8-13].

The biological targets of Pb are the neurological, renal and cardiovascular systems. However, the biological effects of Pb exposure are particularly injurious to the developing brain of children. Pb uniquely acts directly on neurons of the central nervous system (CNS) and affects their neurite development, morphology, ionic channels, as well as presynaptic and postsynaptic function [14]. Pb impairs neurons at all stages of development in the frontal cortex [14], which may induce neurocognitive impairment in Pb-exposed children.

Both acute and chronic Pb exposure may cause irreversible neurological impairment and neurobehavioral anomalies in children and adults [15,16]. Although long-term Pb exposure in childhood has been associated with neurocognitive impairment in adulthood [13], the adverse effects of chronic Pb exposure on neurocognitive function over time is less well understood in children.

PbB concentration reflects acute or current Pb exposure because of the short half-life (~ 36 days) [17] of Pb in blood. Serial tests of PbB levels over time in children with a history of chronic Pb intoxication may serve as a useful index or surrogate of cumulative Pb exposure. Recent follow-up studies have shown a decline in Pb exposure levels in children and adults in the La Victoria study area (i.e., current study area) [18-20].

The aim of the present study was to assess the long-term neurocognitive status of children with a history of chronic and high environmental Pb exposure.

METHODS

Participants and Location

The participants in this field study were 28 school children (16 females and 12 males) aged 4.8 to 15.0 years living since birth in the village of La Victoria in Pujilí, Cotopaxi Province, approximately 125 km south of Quito, Ecuador at an altitude of about 2,800 m above sea level. The children were from largely homogeneous families of similarly low socioeconomic and educational status who worked mainly with discarded Pb-acid automobile storage batteries and utility batteries in the production of Pb-glazed ceramics tiles and vases. Both children and adults worked in the Pb-glazing cottage industry. The primary source of Pb exposure in the children living in the study area is the ingestion of Pb-contaminated food and the widespread Pb particulates in contaminated smoke, dust, and soil in the local milieu. Prenatal Pb exposure from maternal blood and bone stores, and Pb exposure in infancy from maternal breast milk are additional avenues of Pb poisoning in these children [20].

This study was approved by the Human Studies Committee (Comité de Bioética) of Universidad San Francisco de Quito. Informed consent was obtained from a parent or guardian of each child prior to testing. The study was conducted under the auspices of Universidad San Francisco de Quito Colegio Ciencias de la Salud, Escuela de Medicina in Quito, Ecuador. The results of this investigation were provided to the parents/guardians of the participants in the study, who were counseled regarding their children's Pb exposure levels. The children were referred to local health officials for medical intervention as needed.

Pb Concentration in Blood

For assessment of PbB, 4 mL of whole blood were drawn from the antecubital vein of the children included in the study using Li-heparin Vacutainer sets, following thorough cleaning of the skin with swabs containing isopropanol. All blood samples were stored in a refrigerated container, and later analyzed for Pb concentration by graphite furnace atomic absorption spectroscopy with Zeeman background correction at the Boston Children's Hospital Medical Chemistry Laboratory.

Neurocognitive Tests

Raven Coloured Progressive Matrices. The Raven Coloured Progressive Matrices (RCPM) was administered two separate times over a period of 3 years to the group of 28 Andean Ecuadorian children at the local school and Centro de Salud. The children were brought to the field-study testing site by their parents or guardians. Instructions for RCPM were given in Spanish, and the test was administered according to the guidelines in the test manual by Ecuadorian psychologists who were trained in administering the RCPM. Testing was conducted in an isolated, quiet environment with sufficient lighting. The RCPM is a language-free measure of visual-spatial skills and non-verbal reasoning that correlates with standard tests of intelligence, such as the Wechsler Intelligence Scale for Children [21]. The RCPM is an untimed test that involves the matching of pattern constructions of increasing complexity. On each test page of the RCPM is a single pattern with a missing piece, and a selection of 6 design pieces, one of which will complete the pattern or fill in the gap. The child is required to examine the 6 individual pieces and select the appropriate missing piece in order to complete the pattern [22,23]. The RCPM has been reported to have negligible cultural bias and to be capable of evaluating the intellectual status of children exposed to toxic chemicals [24-26].

Digit Span Test. The Digit Span subtest of the Spanish version of the Wechsler IV Intelligence Scale [28] was used to evaluate auditory memory/attention in a subsample of 10 children who were available at the time for follow-up testing. The Digit Span is a test of short-term or working memory in which a series of 2 to 9 digits are presented verbally to the participant who then must repeat the numbers in forward and reverse orders during the testing. The Digit Span test may be considered a test of attention, as well as a test of auditory memory, and is standardized for children and adolescents aged 6-years to 16-years-11 months. The instructions and the digits themselves were presented in Spanish in a quiet setting by trained Ecuadorian psychologists. Digit span tests have been used previously to evaluate cognitive performance in Spanish-speaking children with possible exposure to toxic substances, and children with known Pb exposure [29-32]. Both the RCPM and Digit Span tests have been used successfully for field screening of Pb-exposed, remote populations, as well as non-remote populations exposed to Pb [22,23,25, 27, 31-33].

Statistical Analysis

The arithmetic mean, standard deviation, range, median and geometric mean were calculated for PbB concentrations and performance scores on the neurocognitive tests obtained from the participants in the study. Because some of the data (RCPM-2 test data) were significantly positively skewed, differences between group means were analyzed by non-parametric statistical tests. Differences between means were analyzed using the Wilcoxon Signed Rank Test for paired samples. The association between PbB level and RCPM standard scores was analyzed by Spearman rho correlation analysis. All Z and p values reported for the Wilcoxon Signed Rank Test and the Spearman rho correlation coefficient are tied values. An alpha level of ≤ 0.05 was accepted as an indication of statistical significance.

RESULTS

Blood Pb Concentration and Neurocognitive Test Performance

The box plots of Figure 1 show the PbB levels for the two test periods. The mean PbB level of the children in the study group at the time of the first RCPM test (PbB-1) was 47.2 μg/dL (SD: 23.5; range: 5-95; geometric mean: 39.2; median: 42.4). The mean PbB level at the time of the second RCPM test (PbB-2) was 37.4 μg/dL (SD: 23.1; range: 5-94.3; geometric mean: 28.7; median: 37.0). Statistical analysis showed PbB-2 to be significantly lower than PbB-1 (Wilcoxon Signed Rank Test: Z = -3.844; p = .0001), indicating a reduction in mean PbB level over the 3-year test period. The box plots of Figure 2 illustrate the results of the RCPM for the two test periods. Statistical analysis using the Wilcoxon Signed Rank Test revealed RCPM Test-2 performance to be significantly poorer than RCPM Test-1 performance (Z = -2.512; p = .012), showing the equivalent of a 6.2 points drop in visual-spatial IQ over the approximately 3-year test period. Figure 3A,B shows correlation analyses for concurrent PbB and neurocognitive tests (PbB-1 vs. RCPM-1, and PbB-2 vs. RCPM-2). There were no significant association between PbB-1 and RCPM Test-1 (Spearman rho: Z = -1.322; rho = -.257; p = .182). However, PbB-2 and RCPM Test-2 showed a significant association (Spearman rho: Z = -2.808; rho = -.540; p =.005). PbB-1 and RCPM Test-2 also showed a significant relation (Spearman rho: Z = -2.646; rho = -.509; p = .008). PbB-2 and RCPM Test-1 did not show a significant statistical association (Spearman rho: Z = -1.279; rho = -.246; p .200). The mean of PbB-1 and PbB-2 did not show a significant correlation with RCPM Test-1 performance (Spearman rho: Z = -1.216; rho = -.234; p .224). However, the mean of PbB-1 and PbB-2 showed a significant association with RCPM Test-2 performance (Spearman rho: Z = -2.633; rho = -.507; p = .008). Peak PbB level (the higher of the two PbB levels), which occurred in 89% of the PbB-1 cohort, was not significantly associated with RCPM Test-1 performance (Spearman rho: Z = -1.280; rho = -.246; p = .200), but was significantly associated with RCPM Test-2 performance (Spearman rho: Z = -2.781; rho = -.535; p = .005). The majority of the participants showed poorer scores during follow-up. For example, 61% percent of the participants showed poorer scores during the second Raven test. Only 18% of the children showed improvement of their neurocognitive performance during the second test.

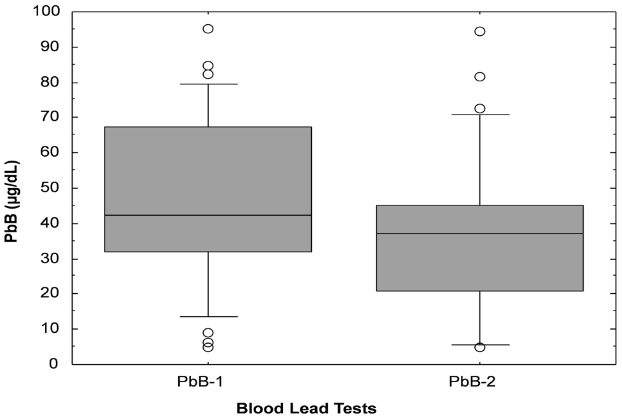

Figure 1. Box plots comparing serial blood lead (PbB) tests on 28 Ecuadorian Andean children living in a lead (Pb) contaminated environment. The boxes contain individual PbB levels between the 25th and 75th percentiles. The horizontal lines inside the boxes represent the 50th percentile. The small horizontal lines above the boxes represent the 90th percentile, and the small horizontal lines below the boxes represent the 10th percentile. The individual data points represent cases above the 90th percentile and below the 10th percentile.

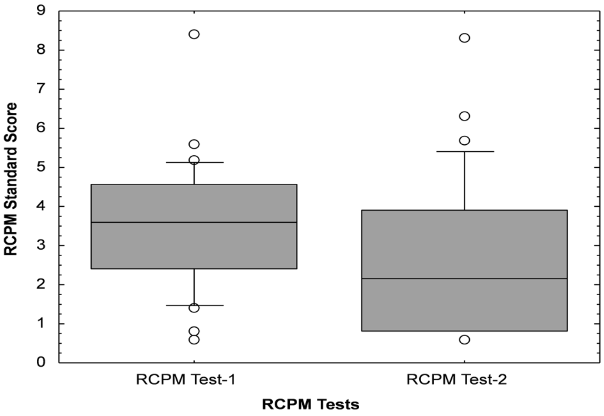

Figure 2. Box plots comparing serial Raven Coloured Progressive Matrices (RCPM) test performance over a 3-year period on 28 Ecuadorian Andean children living in lead (Pb) contaminated communities. Follow-up RCPM Test-2 performance was significantly poorer than the initial test performance (RCPM Test-1) (p = .012).

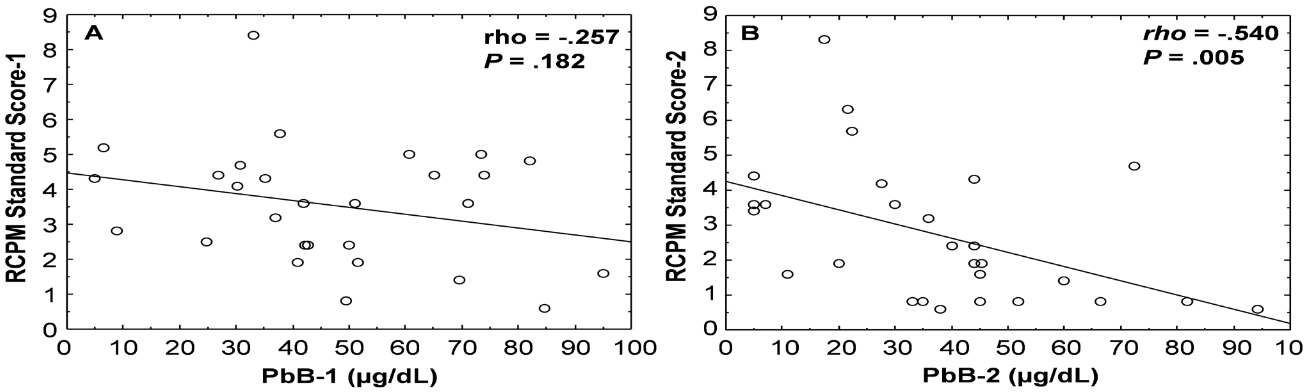

Figure 3. Correlation analyses of the association between performance on Raven Coloured Progressive Matrices (RCPM) and blood lead (PbB) levels in Ecuadorian Andean children. Figure 3A illustrates a non-significant association (Spearman rho correlation coefficients = -.257, p = .182), and Figure 3B shows a significant association (Spearman rho correlation coefficient = -.540, p = .005).

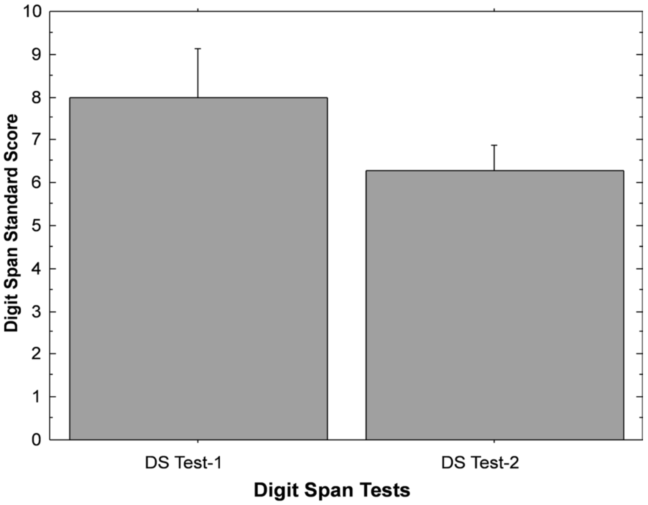

Figure 4. Bar graph comparing the performance of 10 matched Ecuadorian Andean children on two Digit Span tests over a follow-up period of 1 year. The data in the figure indicate a trend toward a decline in auditory memory performance over time, suggesting a cumulative effect of the children's lead (Pb) exposure.

The bar graph of Figure 4 compares the performance of a subsample of 10 Ecuadorian Andean children who were assessed twice on the Digit Span test over a period of 1 year. The data in the graph indicate a trend toward a decline in auditory memory performance over time, suggesting a cumulative or long-term effect of the children's Pb exposure on their neurocognitive functioning.

DISCUSSION

Pb is a well-established neurotoxicant that has been associated with health problems and adverse neurodevelopmental and neurocognitive consequences in both children and adults, including decrements in IQ, and impairment of memory and attention. One of the important questions concerning pediatric Pb poisoning has been whether the adverse neuropsychological or neurocognitive effects of lead exposure are reversible. That is, if PbB levels in children decline as a results of Pb prevention or are lowered as a result of medical treatment, will there be an improvement in neurocognitive performance or functioning? Some earlier studies indicated that the neurocognitive deficits associated with Pb exposure were ameliorated or at least partially reversed with time or with medical treatment as PbB levels declined [34-38]. More recent studies of Pb-exposed children, however, indicate that Pb-related neurocognitive impairments are generally persistent and irreversible [39-43]. Case profiles of several Ecuadorian children living in the same study area as the participants in the current study also suggested that neurocognitive performance improved as PbB levels declined [23]. In order to assess this further, the present study monitored the neurocognitive performance of Ecuadorian children with long-term or lifetime Pb exposure, but declining PbB concentrations, to determine if there was improvement in their neurocognitive status.

The children examined in this study live in an environment of high Pb contamination, and are exposed to Pb-contaminated dust, soil, and air particulates from local Pb-glazing ceramic tile industry. Although a Pb-education and prevention program, and medical intervention have resulted in a decline in pediatric PbB levels in the study area, the average PbB concentration is still higher than the CDC's current reference value of 5 μg/dL [18,44]. The neurocognitive assessment for the current study was conducted at two periods over an average span of three years using the RCPM test of visual spatial intelligence, which is reported to have negligible cultural bias, and efficacy in testing children exposed to toxic substances. A subsample of the same children was followed over a period of a year for assessment of auditory memory/attention using the Digit Span test.

The results of this study revealed a significant decline in blood lead levels between the 2 testing periods. This is consistent with previously reported results showing declining PbB levels in the children in the study area [18]. Unexpected, however, was a concomitant decline in intellectual performance during the follow-up period, as demonstrated by significantly lower standard scores on a measure of visual spatial intelligence, and a trend toward poorer scores on the Digit Span test of auditory memory/attention. That is, neurocognitive performance deteriorated over time. Some studies of occupationally Pb-exposed adults have shown progressive adverse neurocognitive effects, including verbal (auditory) memory deficits, long after initial Pb exposure [45,46]. How this relates to progressive decline in cognitive function in Pb-exposed children is not clear at this time. The Port Pirie Cohort study, which has followed children with Pb exposure into adulthood, showed small associations between pediatric Pb exposure and cognitive development, IQ, and mental health problems [47]. The worsening neurocognitive performance observed in the present study suggests that long-term Pb exposure has an adverse cumulative effect on neurocognitive functioning in the Andean children, which is probably irreversible. Because of the progressive decline in neurocognitive functioning over time, it is important that the cognitive status of the children in this Pb-contaminated environment be continually monitored. It is also important to replicate the current results on a larger number of children to make sure that the results are representative of the Pb-contaminated communities as a whole.

The current study used two PbB measurements over a period of three years as quantities to estimate long-term Pb exposure in this Andean Ecuadorian population. As mentioned previously, the children in the current study have lived all of their lives in the Pb-glazing enclave, and consequently have life-long exposure to occupational environmental Pb. Because Pb in blood has a relatively short half-life of about 36 days [17], it reflects current or acute Pb exposure.

Measurement of bone Pb stores using the *in vivo* X-ray fluorescence (XRF) technique would perhaps have been a more precise method to observe long-term PbB effects on neurocognitive functioning because bone Pb has a half-life of years to decades [48,49]. However, the *in vivo* X-ray fluorescence bone Pb measurement methodology was not feasible in this field study in the Andes Mountains, as special equipment and specially trained personnel are required for this technique [50]. Furthermore, the sensitivity of this technique with children is not fully established, and it is unclear whether this bone Pb measurement procedure is a measure of cumulative Pb in children [51]. More recent advances with portable *in vivo* X-ray fluorescence for bone Pb measurement are still being refined for use in the field [51,52].

A possible weakness of the current study is the small sample size, but the homogeneity of the population is a strength of the study. Because of the small sample size, it is important that the study be replicated on a larger cohort. It is understood that a number of variables, for example, socioeconomic status, nutritional status, maternal intelligence, parental smoking behavior, quality of the caregiving environment, may be considered as possible confounders in the Pb exposure–intelligence association. However, the selection and adjustment of covariates can be a complicated process and may influence the analysis and interpretation of the data [53-56]. In this translational field study, obtaining data on possible conventional confounders was not practical. However, because the population of the study area is homogeneous, in that it is of low socioeconomic and education status, the families have similar occupational Pb-glazing practices, and the population has identical environmental Pb-exposure pathways [55], confounding was not considered to have an important effect on the data.

CONCLUSION

In conclusion, follow-up monitoring of neurocognitive performance of children with life-long Pb exposure in their milieu showed poorer visual spatial intelligence and auditory memory over time, suggesting adverse cumulative outcomes on neurocognitive functioning. However, before any firm conclusion can be drawn, further testing with a larger participant sample should be undertaken.

ACKNOWLEDGMENTS

The authors thank Universidad San Francisco de Quito Colegio Ciencias de la Salud, Escuela de Medicina in Quito, Ecuador for continued support of the Ecuadorian Lead exposure project. We thank Dr. Gonzalo Mantilla, Dean of the College of Health Sciences, Universidad San Francisco de Quito Medical School, for ongoing support and advice. We thank Anthony B. Jacobs for excellent technical assistance. Nurse Gladys Pacheco, of the Subcentro de Salud, La Victoria, Ecuador is thanked for assistance. The authors are grateful to the David Rockefeller Center for Latin American Studies at Harvard University for support of this project. We thank Dr. Jeremy Bloxham, Dean of Science at Harvard University; Harvard Biological Laboratories; and Harvard University Health Services.

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Source of Support: Nil, Conflict of Interest: None declared