Blood Lead Levels in Children with Encephalopathy

Archana Patel and Ambarish Athawale

From the Lata Medical Research Foundation, Nagpur, India, Department of Pediatrics, Clinical Epidemiology Unit, Indira Gandhi Government Medical College, Nagpur, India.
Correspondence to: Dr Archana B Patel, 125, Raj Nagar, Opposite Tidke Vidyalaya, Katrol Road, Nagpur 440 013, India.
Manuscript received: July 25, 2007; Initial review completed: January 11, 2008; Revision accepted:November 6, 2008

Objective: To determine the prevalence of elevated blood lead levels (EBLL i.e blood lead ≥10µg/dL, Centers Disease Control criteria) in children with encephalopathy.

Setting: Hospital.

Design: Case control study.

Participants: 100 children, 49 with encephalopathy and 51 consecutive hospital controls.

Outcome measures: Blood lead levels, demographics, clinical, environmental correlates and residual neurological sequel or death at discharge.

Results: 42 (encephalopathy) and 49 (hospital controls) children were available for analysis. The overall (n=91) mean blood lead was 7.88±10.44 µg/dL (range 0.07-67.68 µg/dL). The predictors of EBLL were presence of wasting (P<0.03), anemia (P<0.04), use of surma (P< 0.02), recent removal of house paint (P<0.01) or recently repainted (P<0.01). The mean blood lead levels were significantly higher (P<0.01) in patients of encephalopathy (12.18±13.90 µg/dL) than in controls (4.19±2.84 µg/dL). EBLL was present in 3/17 (17.6%) patients with infective encephalopathy and in 18/25 (72%) with non-infective encephalopathy. The proportion of children with residual neurological sequelae, or death increased when associated with EBLL (0 to 21%, and 69% to 100% respectively).

Conclusion: Children hospitalized with encephalopathy have elevated blood lead levels.

Keywords: *Blood lead, encephalopathy, EBLL, lead poisoning.*

Lead is a common environmental pollutant recognized as an etiologic factor for subtle cognitive and neurological deficits, hypertension, congenital malformations, immunotoxicity, and deficits in growth and development(1). Children are particularly at risk of neurotoxicity, because of increased sensitivity of the developing brain to the pernicious effects of lead(2). Underlying coexisting disease pathology can also enhance the detrimental effect of lead on the neural system(2). Inspite of these known deleterious effects, there is no universal screening program, and public health regulations to prevent its exposure in children remain in abeyance in India(3). Even children admitted to hospitals with neurological symptoms are seldom, if at all, evaluated for blood lead levels. In this study we evaluated the prevalence of elevated blood lead levels (EBLL) in children admitted to the hospital with and without clinical diagnosis of encephalopathy, the determinants of EBLL, and its correlation with the clinical manifestations and neurological outcomes.

Methods

The study was conducted at Indira Gandhi Government Medical College, Nagpur, India over a period of 6 months from October 2000 to April 2001, to determine in hospitalized children presenting with encephalopathy (irritability with altered consciousness or behavioral abnormality, seizures and focal deficits) and the next consecutive patient without encephalopathy, the prevalence of EBLL(Blood lead ≥10 µg/dL by Centers Disease Control criteria)(4). It

Accompanying Editorial: Pages 841-842.

was approved by the ethics committee and consent from parents was taken. Their clinical diagnosis,

demographics (age, sex, caste, family per capita income, qualification of father and mother, and occupational exposure of father or mother to lead), and previously reported environmental risk factors (pica, use of alternative forms of medicine i.e. ayurvedic or homeopathic for a week or more in the past month, eye cosmetics application i.e. 'surma' in the child, sindur (vermilion) use, whether the house was painted, and paint removal done in the past 12 months or repainted in the past 12 months) were recorded. The nutritional status was assessed as stunted (height for age <5th percentile) and wasted (weight for height <5th percentile) using the National Center for Health Statistics standards(5).

Presence of symptoms of encephalopathy, the clinical etiology of encephalopathy namely infectious or non infectious, the modified Glasgow coma scale (GCS) score on admission, the worst GCS score during the illness, and the outcome of the illness *i.e* complete recovery, death or recovery with some neurological sequel (presence of speech, behavior or mood disorders, reduction in intellectual performance, motor deficits, movement disorders at discharge) were recorded. Cerebrospinal fluid studies, serum electrolytes, blood sugar and computerized tomographic scans of head were done for clinical etiology of encephalo-pathy. Baseline hemoglobin and lead was estimated in venous blood obtained in lead free EDTA vacutainers (Becton Dickinson) and analyzed by flameless atomic absorption spectrophotometry (HitachiZ-8000) in parts per billion at a wavelength of 283.3 nm with a slit width of 1.3 nm using the method described by Lagesson, *et al.*(6). The detection rate of lead for the instrument was 1 µg/L, with an average error rate of 5% for reproducibility of results. Result of lead levels was obtained two weeks after the admissions, so none of the children were offered lead chelation.

Data analysis: We estimated the overall prevalence of elevated blood lead levels (EBLL) and the proportion of children in each Center for Disease Control (CDC) risk classes I [(10-14 µg/dL), IIA(15-19µg/dL), IIB(20-44 µg/dL), III(45-69 µg/dL) and IV(≥70 µg/dL)] in all participants(4). EBLL as a predictor of residual neurological sequel or death, after adjusting for other baseline variables was assessed using logistic regression. Using student's

t test for continuous variables, chi-squared test for categorical variables and multivariate linear regression, we assessed predictors of EBLL.

RESULTS

Of the 100 patients studied (49 with encephalopathy and 51 with no encephalopathy) blood lead levels were available for 42 and 49, respectively. Their baseline characteristics are presented in *Table* I. The overall mean blood lead was 7.9±10.4 µg/dL (range 0.07 to 67.7 µg/dL). EBLL was observed in 19 children (20.9%) of whom 8 were in class I (8.8%), 3 in class IIA (3.3%) and 8 children were in class IIB (8.8%). Mean blood lead levels were significantly higher in patients of encephalopathy (12.2±13.9 µg/dL) than in controls (4.2±2.8 µg/dL) ($P<0.01$). Of 42

TABLE 1 BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Variable	Encephalopathy (*n*=42)	No encephalopathy Controls (*n*=49)
Age (mean ± SD)	4.59±3.04 yrs	7.46±3.16 yrs
Income (mean ± SD)	326.90±315.97	182.35±92.1
Fathers occupational exposure present	2 (4.7%)	6 (12.2%)
House paint present	15 (35.7%)	22 (44.9%)
House paint removal	7 (16.7%)	2 (4.1%)
House repainted	7 (16.7%)	1 (2.0%)
Use of ayurvedic/ homeopathic medicine	7 (16.7%)	0
Use of *surma*	31 (73.8%)	9 (18.4%)
Use of *sindhur*	20 (47.6%)	16 (32.7%)
Pica	20 (47.6%)	16 (32.7%)
Wasting	19 (45.2%)	9 (18.4%)
Stunting	18 (42.9%)	33 (67.3%)
Mean blood lead levels (µg/dL)	12.18±13.90	4.19±2.84
Hemoglobin	10.00±0.98	9.56±0.99
CDC category		
Class I	25 (59.5%)	47 (95.9%)
Class IIA	7 (16.7%)	1 (2.0%)
Class IIB	2 (4.8%)	1 (2.0%)
Class III	8 (19.0%)	0

WHAT IS ALREADY KNOWN

- Children are particularly at risk of neurotoxicity, because of increased sensitivity of the developing brain to elevated blood lead levels.

WHAT THIS STUDY ADDS

- In hospitalized children, those with encephalopathy had higher mean lead levels had and poorer outcome when associated with elevated blood lead levels.

---

children with encephalopathy, 17 had blood lead levels more than 10 µg/dL as compared to only 2 amongst the controls (*P*<0.01). Patients with encephalopathy were more likely (*P*<0.01) to be in higher CDC class.

On admission, 16 patients had infectious encephalopathy (8 of acute pyogenic, 4 of tuberculosis, 3 of viral encepholpathy and 1 of cerebral abscess) and 26 were of non infectious etiology (1 of Reye, 8 of anoxic, 7 of febrile and 10 of metabolic encephalopathy). EBLL was present in 3/17 (17.6%) patients with infective encephalopathy as compared to 18/25 (72%) patients with non-infective encephalopathy. Among patients of encephalopathy, 10/49 (23.8%) children had residual neurological sequel and 5 (11.9%) children died; rest 26(61.9%) children recovered completely on discharge. The mean blood lead levels were higher in children with residual neurologic sequel or death (13.61±14.72 µg/dL) as compared to those who recovered completely (11.69±13.83 µg/dL), but this difference was not statistically significant. Infective encephalopathy (OR 33.3; 95% CI 2.8, 100) was most predictive of poor recovery, after adjusting for age, wasting, the worst GCS and BLL. Residual neurological sequel and death in patients with infective encephalopathy was 9/13(69%) and rose to 100% (all three children died) when associated EBLL. In non infective encephalopathy residual neurological sequel or death was absent without EBLL and rose to 3/14 (21%) with EBLL.

The predictors of EBLL were presence of wasting (*P*=0.03), anemia (*P*=0.04), recent removal of house-pain (*P*=0.009), recent repainting (*P*= 0.003) and use of surma (*P*=0.02). There was no association of EBLL with the use of ayurvedic or homeopathic medicines, sindur (vermilion), pica, fathers' occupational exposure, caste or income.

DISCUSSION

The overall prevalence of EBLL was 20.9% in hospitlalized children, 40.5% in children who presented with encephalopathy as compared to 4.1% in controls. Of the patients with encephalopathy, those with non-infective encephalo-pathy were more likely to have EBLL than those with infective encephalopathy. In children with non-infective as well as with infective encephalopathy, the proportion of children with residual neurological sequel or death increased when associated with EBLL (0 to 21%, and 69% to 100%, respectively). The lead levels most likely to result in neurotoxicity are still debated and has been observed at lower levels(7). This study is only the third in India to report BLL in children with encephalopathy. The mean blood lead level in children with encephalopathy (12.18±13.90 mg/dL) was significantly higher as compared to controls and consistent to the observations made in the previous two studies(8,9). So EBLL (even Class II or III poisoning) may exacerbate the neurological damage of coexisting non infective or infective pathology of the nervous system. Oxidative stress and free radical generation was reported to be the mode of neurological lead toxicity. Studies done in animals suggest that EBLL predisposes and aggra-vates infections by enhancing B cell activities and Th2 proliferation, and inhibits Th1 prolife-ration(10). In rodents, it enhanced susceptibility to endotoxin shock and lipopolysaccharide (LPS) lethality in gram-negative infections by increasing the secretion and uptake of tumor necrosis factor-alpha (TNF-alpha) and increasing other proinflam-matory cytokines(11). This increased concentration of proinflammatory cytokines (IL-1 beta and TNF-alpha IL-6) in the cerebrospinal fluid correlates well with presence of neurologic sequel or death in patients of infectious meningoencephalitis(12,13). The limitation of this study is that we did not assess

levels of proinflammatory cytokines and markers of oxidative stress predictive of poor outcome. Children with EBLL would not only have an increased susceptibility to infections but also be at a greater risk of encephalopathy at lower levels of blood lead during infective and febrile episodes. However this causal relationship could not be studied in this cross-section of patients.

Predictors of EBLL were nutritional wasting, anemia and environmental exposures such as use of surma and recent removal of house paint or repainting, which were similar to those reported previously and indicate the need for implementing guidelines for preventing the use of lead based paints and eye cosmetics like surma(5).

In conclusion, developing countries like India where malnutrition, anemia and the incidence of infections is high, universal screening and early chelation especially in co-morbid neurological illness could prevent morbidity and mortality. The therapeutic benefits of investigating for EBLL and lead chelation in children of any encephalopathy, even in lower CDC classes, need further exploration. Additionally, public health regulations are also needed to reduce environmental exposures through paint and cosmetics.

REFERENCES

1. Goyer RA. Lead toxicity: from overt to sub clinical to subtle health effects. Environ Health Perspect 1990; 86:177-181.

2. Lidsky TI, Schneider JS. Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain 2003; 126: 5-19.

3. Patel AB, Williams SV, Frumkin H, Kondawar VK, Glick H, Ganju AK. Blood lead in children and its determinants in Nagpur, India. Int J Occup Environ Health 2001; 7: 119-126.

4. Centers for Disease Control and Prevention. Managing Elevated Blood Lead Levels Among Young Children: Recommendations From the Advisory Committee on Childhood Lead Poisoning Prevention. Atlanta, GA: Centers for Disease Control and Prevention; 2002.

5. Hyattsvile MD. US Department of Health and Human Services. National Center for Health Statistics. Phase 2, Third National Health and Nutrition Examination Survey Data. 1991-1993: Machine readable public–use data tapes, 1996.

6. Lagesson V, Andrasko L. Direct determination of lead and cadmium in blood and urine by flameless atomic absorption spectrophotometry. Clin Chem 1979; 25: 1948-1953.

7. Winneke G, Krämer U. Neurobehavioral aspects of lead neurotoxicity in children. Cent Eur J Public Health 1997; 5: 65-69.

8. Kumar A, Dey PK, Singla PN, Ambasht RS, Upadhyay SK. Blood lead levels in children with neurological disorders. J Trop Pediatr 1998; 44: 320-322.

9. Ahamed M, Fareed M, Kumar A, Siddiqui WA, Siddiqui MK. Oxidative stress and neurological disorders in relation to blood lead levels in children. Redox Rep 2008; 13: 117-122.

10. Heo Y, Parsons PJ, Lawrence DA. Lead differentially modifies cytokine production in vitro and in vivo. Toxicol Appl Pharmacol 1996; 138:149-157.

11. Flohe SB, Bruggemann J, Herder C, Goebel C, Kolb H. Enhanced proinflammatory response to endotoxin after priming of macrophages with lead ions. J Leukoc Biol 2002; 71: 417-424.

12. Jain M, Aneja S. CSF interleukin-1 beta, tumor necrosis factor-alpha and free radicals production in relation to clinical outcome in acute bacterial meningitis. Indian Pediatr 2000; 37: 608-614.

13. Aiba H, Mochizuki M, Kimura M, Hojo H. Predictive value of serum interleukin-6 level in influenza virus-associated encephalopathy. Neurology 2001; 57: 295-299.