CLINICAL AND LABORATORY OBSERVATIONS

Symptomatic lead poisoning in infancy: A prospective case analysis

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This report of a case of symptomatic lead poisoning in infancy reinforces the need for continued vigilance in screening and the application of effective therapies to prevent serious physiologic, neurocognitive, and behavioral sequelae. Furthermore, this case illustrates the efficacy of repeated courses of outpatient succimer therapy in limiting a rebound in blood lead concentrations. (J Pediatr 2000;137:568-71)

It has been fairly well established that exposure to lead at low to moderate levels is associated with modest declines in psychometric intelligence and may also increase a child's risk for academic failure and conduct disorder.[1] However, there are virtually no comprehensive prospective neuropsychologic data on the development of children who survive acute symptomatic lead poisoning.

The last known case of fatal pediatric lead poisoning in the United States occurred in 1990.[2] Symptomatic lead poisoning is now rare, and one may be tempted to assign the disease to the dusty annals of medical history. Here, we report a recent and unusually detailed case analysis of symptomatic lead poisoning, its treatment, and central nervous system manifestations from infancy through early childhood. The purpose of this account is to draw attention to the efficacy of outpatient succimer therapy after hospitalization for frank lead intoxication and the signature neurodevelopmental manifestations of lead toxicity presented by this patient.

CASE REPORT

The patient, a 14-month-old girl, was enrolled in the screening phase of the Treatment of Lead-Exposed Children randomized clinical trial for asymptomatic lead intoxication.[3] The TLC study is examining the developmental benefits of outpatient succimer (dimercaptosuccinic acid) therapy versus a placebo in children with blood lead concentrations in the range of 20 to 44 μg/dL. Lead in blood was measured by atomic absorption spectrometry at the United States Centers for Disease Control and Prevention. Children returned for clinic visits at 7, 28, and 42 days after the beginning of each course of therapy. Participants could receive up to 3 courses of treatment. After treatment was completed, children were seen at 3-month intervals for clinical examination and blood lead measurement during the first 2 years of follow-up and at about 4-month intervals in the third follow-up year. After a baseline examination, follow-up psychometric assessments were

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TLC Treatment of Lead-Exposed Children

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performed at 6 months, 18 months, and 3 years after randomization.

The infant described in this case report was born at 41 weeks' gestational age with a birth weight of 3572 g. Her family consists of a single mother with a high-school education and full-scale IQ of 102 who is receiving public assistance. Social history is negative for adverse environmental factors. Results of laboratory studies included blood lead concentration of 42 μg/dL, ferritin level of 6 μg/L, and normal complete blood count. Vitamins and minerals were prescribed daily. The second preenrollment visit revealed no overt or clinical laboratory evidence of lead intoxication, blood lead concentration of 41 μg/dL, and ferritin level of 19 μg/L. The patient was enrolled in TLC and remained free of symptoms while receiving 3 courses of active study drug (succimer) during the following 5 months. All subjects in TLC received an extensive environmental inspection for lead sources and a thorough cleaning of the primary residence before treatment.

On follow-up at age 21 months, the patient's blood lead concentration was reported to be 122 μg/dL. This was approximately 50 days after the last administration of succimer therapy according to the TLC protocol.[3] The patient's increased lead ingestion appeared to be due to the structural collapse of a plaster ceiling in the family's apartment residence. She was hospitalized within 24 hours, and just before the initiation of treatment, her blood lead concentration was reported by the toxicology laboratory at the University of Cincinnati to be 142 μg/dL. History revealed sporadic emesis, abdominal pain, and loose stools. In recent days the child had fallen frequently, run into walls, and had difficulty climbing stairs. The TLC developmental examiner, who was unaware of the child's blood lead level or treatment status, also noted these behaviors in a scheduled follow-up assessment that occurred just before hospitalization. Findings on physical examination were normal. Treatment was begun with British Antilewisite, 75 mg/m^2, administered intramuscularly every 4 hours and continued for 3 days. Treatment with edetate calcium disodium ($CaNa_2EDTA$), 1000 mg/m^2, given intravenously was begun 4 hours later and continued for 5 days. Treatment was well tolerated, and the patient was discharged to receive succimer, 200 mg, twice daily (31.5 mg/kg/d). This dose, which is somewhat lower than that recommended for primary therapy,[4,5] was based on body surface area in compliance with the TLC protocol.[3] Lead-safe housing was assured before discharge by examining the home for lead hazards and performing clean-up and dust control measures.[3] Compliance was acceptable as judged by parental report and capsule count. Succimer therapy was continued for 25 days on an outpatient basis. Her appetite returned, and her motor coordination seemed to improve. A blood lead concentration of 39 μg/dL obtained at 24 months resulted in a 19-day course of succimer therapy (Figure). During treatment with succimer, a blood lead concentration of 21 μg/dL was observed at 25 months. By 30 months her blood lead concentration had dropped to 16 μg/dL. However, during a scheduled visit at age 32 months, her mother noted abdominal pain, loose bowel movements, and increased falling. At that time her blood lead concentration had risen to 42 μg/dL, coinciding with the family's return to their previous lead-hazardous residence. The family was moved to a lead-safe public housing unit. A standard 19-day course of succimer was again begun, and an appropriate response to treatment was noted. At a routine follow-up visit at age 36 months, her mother noted an increased activity level. During physical examination the patient was in constant motion and exhibited oppositional behavior. Her blood lead concentration at that time was 31 μg/dL. Routine follow-up was continued according to the TLC protocol thereafter, and at a late developmental follow-up visit at age 4 years, her blood lead concentration was 20 μg/dL.

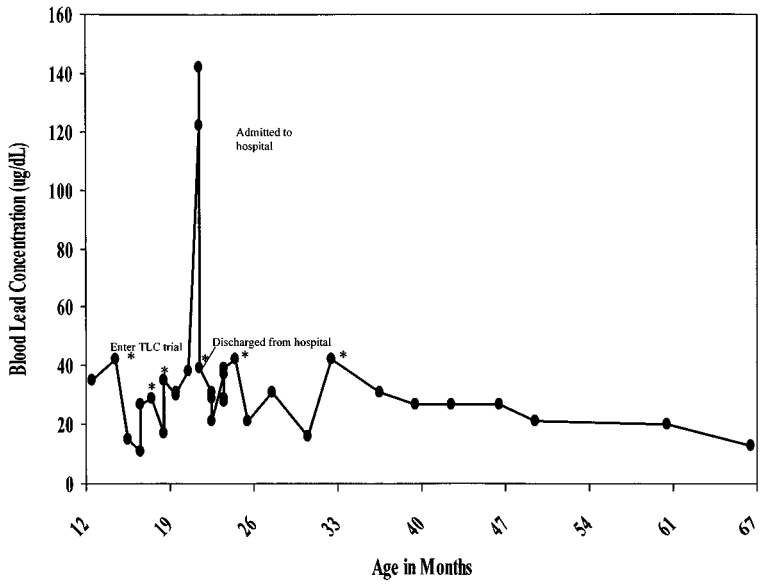

Figure. Longitudinal blood lead profile of a lead-poisoned patient followed up from 1 through 5½ years of age. *Asterisk* denotes initiation of courses of succimer therapy.

Extensive neurodevelopmental data have been gathered since the patient was approximately 1 year of age. Since she entered the TLC trial, standardized measures of cognitive and motor functioning have been administered at regular intervals, including the Bayley Scales of Infant Development-II,[6]

Table. Neurodevelopmental profile of a lead-poisoned patient followed up from 1 through 5 years of age

Age at assessment	Test	Standard score	Blood lead concentration (μg/dL)
15 mo	BSID2 Mental Development Index	99	42
21 mo	BSID2 Mental Development Index	82	122
24 mo	BSID2 Mental Development Index	76	42
32 mo	BSID2 Mental Development Index	89	42
51 mo	WPPSI-R		21
	Full-Scale IQ	83	
	Verbal IQ	88	
	Performance IQ	81	
	CPRS-R short form*		
	Oppositional	87	
	Hyperactivity	87	
	ADHD Index	84	
52 mo	NEPSY		
	Attention/Executive Functions	81	
	Language	91	
	Sensorimotor	72	
	Visuospatial	59	
	Memory	101	
61 mo	BOTMP		21
	Balance	7	
	Fine-Motor Composite	28	

BSID2, WPSSI-R, and NEPSY standard scores are normed to a mean of 100 and SD of 15. The BOTMP Balance subscale is normed to a mean of 15 and SD of 5, and the Fine-Motor Composite is normed to a mean of 50 and SD of 10.

BSID2, Bayley Scales of Infant Development-II; *WPPSI-R,* Wechsler Preschool and Primary Scales of Intelligence-Revised; *CPRS-R,* Conners' Parent Rating Scale-Revised; *NEPSY,* NEPSY–A Developmental Neuropsychological Assessment; *BOTMP,* Bruininks-Oseretsky Test of Motor Proficiency.

*T-Scores (scores above 70 are considered clinically significant).

Wechsler Preschool and Primary Scales of Intelligence-Revised,[7] NEPSY–A Developmental Neuropsychological Assessment,[8] Bruininks-Oseretsky Test of Motor Proficiency,[9] postural sway assessment,[10] and Conners' Parent Rating Scale-Revised.[11]

Data from several large epidemiologic studies suggest that moderate exposure to lead during the first 5 years of life is associated with deficits in attention/executive functions, visual-spatial skills, fine-motor coordination, balance, and social-behavioral modulation.[12] The individual neurobehavioral profile of this patient matches these findings from studies of lead-exposed children (Table).

At baseline, the patient achieved a Bayley Scales of Infant Development–II Mental Development Index of 99, which is only 1 point below the population mean. It should be acknowledged that, at baseline, the child had a blood lead concentration in the range associated with neurotoxicity. Thus her scores at this point in time may already reflect some lead effects. However, at 21 months, and concurrent with a dramatic elevation in her blood lead concentration, her index score dropped more than 1 SD and dropped again when she was assessed at 2 years. Some recovery was evident at 32 months. However, at approximately 4 years of age, her full-scale IQ was more than 1 SD below the mean with the greatest weakness in performance IQ, which primarily reflects deficits in perceptual-motor and visual-spatial skills. The results of the Wechsler Preschool and Primary Scales of Intelligence–Revised are confirmed by the NEPSY assessment on which the patient had scores in the clinically significant range for the sensorimotor and visuospatial core domains. Her performance on subtests assessing attention/executive functions was also poor, as reflected in a low standard score on this subscale. At the same time, there was a relative sparing of linguistic and mnemonic skills. Standard scores on the Bruininks battery were lowest in the areas of balance and fine-motor abilities, at approximately 2 SDs below the population means. In comparison with children with low blood lead levels, this patient also displayed significantly greater postural instability as assessed by a microprocessor-based strain-gauge force platform system.[13] The patient's performance was particularly impaired in the "eyes-closed" test condition on a compliant surface where there was at least one incident of falling during the test, implying difficulty in using the vestibular system appropriately for the maintenance of upright balance.

In the area of social-behavioral conduct, the patient had clinically significant scores on the Conners' Parent Rating Scale–Revised Oppositional, Hyperactivity, and Attention-Deficit Hyperactivity Disorder Index. The parental report was confirmed by the developmental examiner who noted hyperactive, aggressive, and oppositional behavioral characteristics during the assessment session.

DISCUSSION

Symptomatic lead poisoning is now a rare malady. However, cases such as the one described here indicate the need for continued vigilance to prevent future fatalities or serious neurodevelopmental deficits. This case illustrates the efficacy of outpatient succimer therapy in the prevention of rebound in blood lead levels as a result of redistribution from bone and soft tissue stores after chelation therapy with combined British Antilewisite/EDTA.[14] The patient also displayed a pattern of cognitive and social-behavioral deficits that matches the pattern found in a number of well-designed neuroepidemiologic studies of lead and child development.[12]

Some observers contend that the evidence for a specific syndrome of neuropsychologic delays or deficits caused by lead exposure is presently insufficient.[15] We agree that a behavioral end point with sufficient sensitivity and specificity that can be used as a screening instrument to identify infants or children with lead-related cognitive deficits does not exist. However, data from several neuroepidemiologic studies are suggestive of a specific pattern of deficits in lead-exposed children, and this case provides an interesting example.

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