Neuroendocrine Effects of Toxic and Low Blood Lead Levels in Children

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ABSTRACT. From 3 million to 4 million children in America have lead poisoning. This environmental toxin affects 1 in every 6 children younger than 6 years of age in the United States. The marked effects of lead toxicity on the central nervous system are well known, ie, lowering IQ and impairing memory, reaction time, and the ability to concentrate. Children are at greatest risk for the central nervous system effects of lead because the central nervous system is at its peak in development during the first few years of life. The negative correlation of stature and blood lead level (bPb) found in the National Health and Nutrition Examination Survey directed the authors to evaluate the possible neuroendocrine effects of this toxin in children. Twelve children were studied during toxic (≥40 μg/dL) and low bPb (<40 μg/dL). Classic provocative stimuli, L-dopa (15 mg/kg by mouth) and insulin (0.1 U/kg given intravenously), were used to determine human growth hormone (hGH) responses during toxic bPb and after chelation therapy in six of the subjects. An additional four subjects were studied during low bPb. In two patients LGH levels were determined every 20 minutes for 24 hours during toxic bPb. Thyroid-stimulating hormone and prolactin responses to thyrotropin-releasing hormone were also determined. All children studied showed growth retardation during toxic bPb. Mean peak hGH responses to provocative stimuli were lower during toxic bPb, but the responses were all within normal limits. The mean 24-hour hGH values were low in the two patients (0.8 ± 0.2 [SE] ng/mL and 2.0 ± 0.8 ng/mL) studied compared with normal control patients (6.4 ± 0.3 ng/mL). Insulin-like growth factor I values showed an inverse correlation with toxic blood bPb, up to 40 μg/dL. Basal thyroid-stimulating hormone, prolactin, thyroxine, and triiodothyronine concentrations were not affected by bPb. In addition, thyroid-stimulating hormone and prolactin responses to thyrotropin-releasing hormone were not affected by toxic or low bPb. Cortisol responses to insulin-induced hypoglycemia were normal ($P \leq .05$). These observations, taken together, confirm the inadequacy of acute hGH responses to secretagogue as a reliable indicator of hGH secretion and indicate that lead-induced short stature may be due to diminished hGH secretion, which in turn results in reduced insulin-like growth factor I secretion, or that Pb may also directly inhibit insulin-like growth factor I formation. *Pediatrics* 1992;90:186–189; *lead toxicity, neuroendocrine effects, growth.*

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ABBREVIATIONS. bPb, blood lead level(s); hGH, human growth hormone; IGF-I, insulin-like growth factor I; TSH, thyroid-stimulating hormone; PRL, prolactin; TRH, thyrotropin-releasing hormone; IV, intravenous; T_4, thyroxine; T_3, triiodothyronine.

That lead is an environmental toxin is an ancient observation. However, it was only recently that short stature was ascribed as a specific consequence of lead toxicity in children. The investigators' analysis of the National Health and Nutrition Examination Survey 1976–1980 data on 2695 children aged 6 months–7 years revealed a significant negative correlation of blood lead level (bPb) between 5 and 35 μg/dL with height, weight, and chest circumference.[1] The correlation was independent of the significant growth effects of sex, race, total dietary protein or calories, hematocrit, or transferrin saturation. In this analysis the three growth parameters did not relate to family income or urbanization; dietary carbohydrate, potassium, phosphorus, vitamins A and C, niacin, or riboflavin; or serum levels of albumin, copper, iron, or zinc. This significant negative correlation of stature and bPb prompted us to undertake a systematic study to elucidate the possible neurohormonal mechanism(s) by which lead-induced short stature may be caused. The purpose of our present study was to determine various aspects of human growth hormone (hGH) secretion in a group of children (1) while they had bPb in the toxic range of ≥40 μg/dL and (2) when the bPb was <40 μg/dL. In addition, basal thyroid hormone and insulin-like growth factor I (IGF-I) concentrations were determined. Cortisol responses to hypoglycemia were measured as well as thyroid-stimulating hormone (TSH) and prolactin (PRL) responses to thyrotropin-releasing hormone (TRH).

METHODS

Patients

A total of 12 children, aged 2–5 years, from the Omaha Lead and Poison Prevention Program were studied during toxic and low bPb. The toxic bPb was treated with $CaNa_2$-ethylenediaminetetraacetic acid at a dosage of 1000 mg/m^2 per day given intravenously for 5 days in 6 of the subjects.[2] Height was measured at 2- to 3-month intervals during toxic and low bPb. The mean of three height determinations was used. The ranges of toxic and low bPb were 41 to 72 μg/dL and 0 to 30 μg/dL, respectively.

Study Design

Classic provocative growth hormone stimuli, L-dopa (15 mg/kg, given by mouth) and insulin (0.1 U/kg, intravenous [IV]), were used during toxic bPb and 24 to 48 hours after the 5-day chelation therapy in six of the subjects. An additional four subjects were studied during low bPb. Levels of hGH were determined every 20

minutes over a 24-hour period in two additional patients during toxic bPb. Basal and hourly IGF-I determinations during provocative hGH testing were made during toxic bPb and low bPb.

Other Hormones

Basal thyroxine (T_4), free T_4, and triiodothyronine (T_3) levels were measured in all subjects. TSH and PRL responses to TRH (7 μg/kg, IV) in five subjects were determined. Cortisol responses to insulin (0.1 U/kg, IV)-induced hypoglycemia were measured in the same five subjects.

Hormone Assays

Serum levels of hGH, PRL, and cortisol were determined by previously described radioimmunoassays.[3-5] Serum T_4 was measured by a standard double antibody radioimmunoassay (T_4 standard and antiserum from Endocrine Sciences; iodine 125 from Abbott Laboratories, Abbott Park, North Chicago, IL). Free T_4 and T_3 were measured by commercial kits (Clinical Assays, Travenol Genentech Diagnostics). Serum TSH values were measured through reagents provided by the Hybritech Company on a one-step immunoradiometric procedure. Unextracted IGF-I samples were measured by commercial kits (Nichols Institute).

Statistical Analysis

Student's paired and unpaired *t* tests and multiple linear regression analysis were used to determine significance of hormone responses and growth responses ($P < .05$). Pulsatile growth hormone measurements were analyzed by the DETECT program provided by the Laboratory of the Theoretical and Physical Biology of the National Institutes of Health.

RESULTS

Effects on Growth

Figure 1 shows the growth rate of six children during toxic and low bPb. The mean growth rate during toxic bPb was 5.8 ± 1 (SE) cm/y in comparison with 11.0 ± 2 cm/y during low bPb.

Of the six patients who showed toxic bPb values, five children were 2.0 to 3.0 years of age (group 1) and the sixth patient was 1.5 years old at the time of the study. The growth rate of group 1 averaged 4.2 ± 0.9 cm/y before chelation therapy and 9.0 ± 0.9 cm/y at low bPb following chelation therapy. Normal growth rate for this age is 12.5 cm/y. The sixth patient grew at the rate of 8.3 cm/y before chelation and 12.0 cm/y after therapy (normal 25 cm/y).

Of the four patients who had low bPb and did not receive chelation therapy, three were 2.0 to 2.3 years of age (group 2) and the remaining patient was 5.2 years old. The growth rate of group 2 averaged 8.9 ± 1.0 cm/y. The growth rate for the 5.2-year-old patient was normal (7.0 cm/y).

Changes in weight were also evaluated in the study. During toxic bPb, the average weight change was 41.7% ± 9.5% on the growth chart. During low bPb the average and range of weight change were 51% ± 7.9% (15% to 90%). Three of the six patients who had chelation therapy showed an increment of 10% to 25% in weight percentiles after chelation. The remaining three patients showed no change.

Effects on hGH and IGF-I Concentration

In Fig 2 the peak hGH values are shown in response to an L-dopa and insulin test in six children during toxic and low bPb. The peak hGH response was significantly lower in children with toxic bPb (25 ± 7 ng/mL) compared with the peak response in children with low bPb (42 ± 8 ng/mL).

The mean 24-hour pulsatile growth hormone parameters are demonstrated in the Table and in Figs 3 and 4. These hGH values were compared with values from our "short" normal children and with values from our children with growth hormone neurosecretory dysfunction. The mean 24-hour hGH values of the two children studied during toxic bPb were significantly lower than those of our normal children and were comparable with the low values of children with growth hormone neurosecretory dysfunction.[6] Nocturnal peak hGH values and areas under the pulse were also lower during toxic bPb in the two children studied.[7]

The mean IGF-I values were also significantly lower during toxic bPb (0.4 ± 0.01 μU/mL) compared with

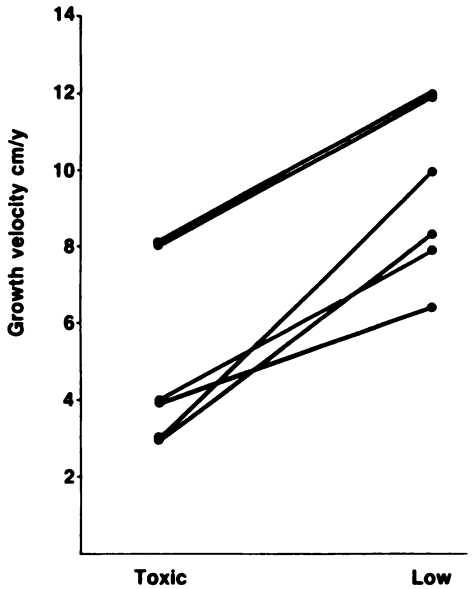

Fig 1. Growth velocity during toxic and low blood lead levels in six children who received chelation therapy ($P \leq .05$).

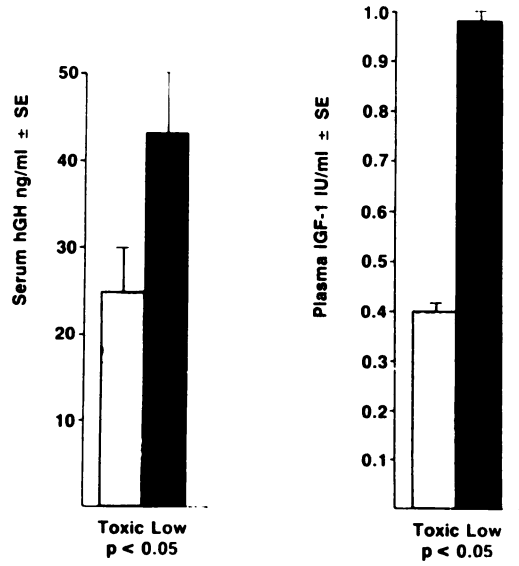

Fig 2. Comparison of peak human growth hormone (hGH) and insulin-like growth factor I (IGF-I) responses to L-dopa insulin test during toxic and low blood lead levels ($P \leq .05$).

TABLE. Growth Hormone Pulse Parameters in Two Lead (Pb) Toxicity Patients (Prechelation) Compared With Short Normal Children and Children With Growth Hormone Neurosecretory Dysfunction (GHND)*

	Corrected Age, y	24-Hour hGH Conc, ng/mL	Nocturnal Peak hGH Conc, ng/mL	No. of Pulses	No. of Nocturnal Pulses	Pulse Conc, ng/mL	Sum AUP, ng/mL-min	Sum AUP-N, ng/mL-min
Patient 1 (Pb = 66 μg/dL)	5.1	2.0 ± 0.8	17.8	1.0	1.0	9.4 ± 5	461.2	461.2
Patient 2 (Pb = 81 μg/dL)	2.3	0.77 ± 0.2	0.8	1.0	0	6.5	161.0	NA
Short normal (n = 20)	7.1 ± 0.6	6.4 ± 0.3	38.2 ± 3	6.0 ± 0.5	2.8 ± 0.2	9.9 ± 0.6	1084.3 ± 97	1433.0 ± 129
GHND (n = 8)	6.8 ± 1.1	2.1 ± 0.3	15.8 ± 4.4	2.8 ± 0.4	1.8 ± 0.4	6.7 ± 0.8	461.9 ± 120	590.0 ± 235.8

* Results are absolute values or mean ± SE. A pulse is defined as two or more human growth hormone (hGH) concentrations greater than 3 standard deviations above the assay coefficient of variation. Sum of area under the pulse (Sum AUP) is determined by the trapezoidal area under each pulse. Sum AUP-N refers only to those pulses which occurred during sleep. NA, not applicable.

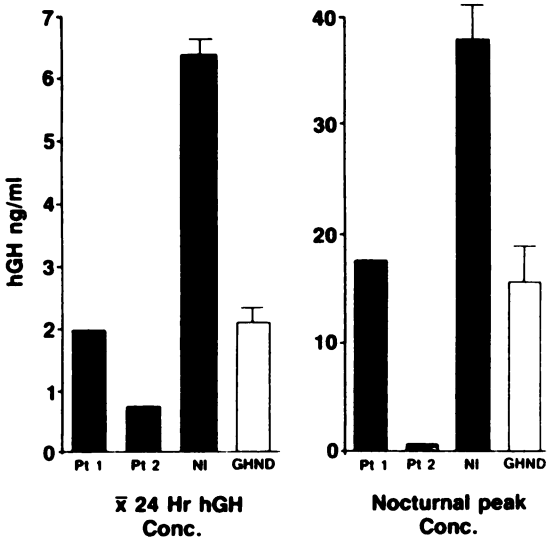

Fig 3. Mean ($\bar{X}$) 24-hour human growth hormone (hGH) concentrations and nocturnal peak hGH concentrations of two children (patients 1 and 2) during toxic blood lead levels, compared with short normal children (NI) and children with growth hormone neurosecretory dysfunction (GHND).

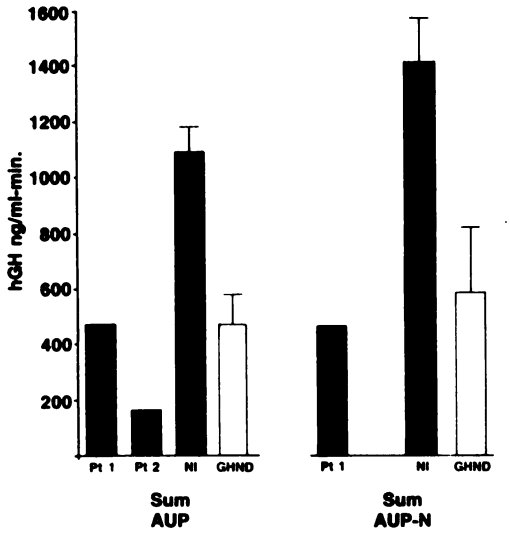

Fig 4. Sum of the area under the pulse (Sum AUP) and Sum-AUP-N (at night) in two children (patients 1 and 2) during lead toxicity, compared with short normal children (NI) and children with growth hormone neurosecretory dysfunction (GHND). hGH, human growth hormone.

values during low bPb (0.98 ± 0.2 μU/mL) (Fig 2). Further, IGF-I values showed an inverse correlation with toxic bPb to a Pb value of <40 μg/dL ($r = -.68$) (Fig 5). No further decrement in IGF-I concentration occurred in blood lead samples of >40 μg/dL. TSH and PRL responses to TRH during toxic and low bPb were not affected by bPb.

DISCUSSION

The neuroendocrine studies of these children indicate that lead-induced short stature may be due to diminished hGH secretion, which, in turn, results in reduced IGF-I secretion, or that lead may also directly inhibit IGF-I formation. Although the mean peak hGH responses to provocative stimuli were lower during toxic bPb, they were not abnormally low. This confirms the inadequacy of only acute hGH responses as a reliable indicator of hGH secretion. The 24-hour hGH secretory profile in the two children studied showed markedly reduced values. The hGH values were similar to those of our children who have neurosecretory dysfunction in growth hormone release. These data imply an effect by lead on the pulsatile hGH and/or growth hormone-releasing hormone secretion. Caloric intake can influence hGH and IGF-I

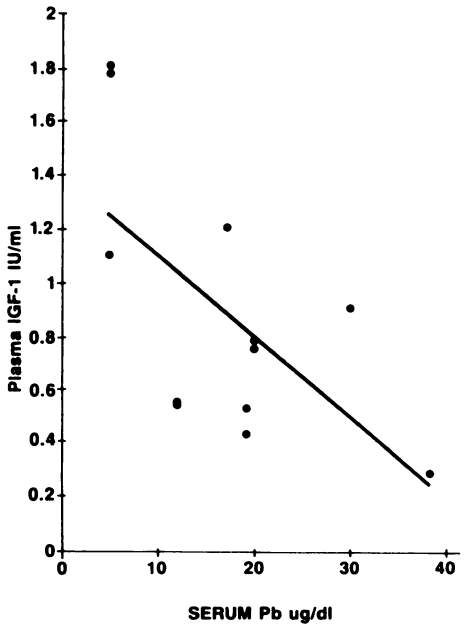

Fig 5. Comparison of insulin-like growth factor I (IGF-I) concentrations during toxic and low serum lead (Pb) levels.

secretion. Although caloric intake was not monitored, the children in this study were not underweight for their height. Three children who received chelation therapy did show incremental changes in weight percentile after therapy.

In an earlier study, blunted TSH response to TRH was noted during toxic bPb.[8] The clinical endocrine studies in two children showed that TSH release after TRH stimulation was impaired by bPb in the range of 19 to 72 μg/dL. These data were consistent with the deficient TSH response to TRH found in about half of adult lead workers with PbB in the range of 30 to 60 μg/dL.[9,10] In the present study, TSH and PRL responses were unaffected by toxic bPb. Hormonal secretion in vivo may be affected not only by blood lead concentration, but also by the duration of exposure to the lead. The central nervous system's dependence on normal thyroidal function in the first 2 years of life for normal development warrants careful evaluation of the effect of both low and toxic PbB on the hypothalamic-pituitary-thyroidal axis.[11,12] Further, the need for continued normal hGH secretion to maintain normal growth warrants careful and continued evaluation of these children during lead toxicity.

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