The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Volume 348:345-347 January 23, 2003 Number 4

Increased Body Lead Burden — Cause or Consequence of Chronic Renal Insufficiency?

Philip A. Marsden, M.D.

Greek physicians first recognized the association between exposure to lead and disease over two millennia ago. The sources of lead have changed since ancient times, but exposure is still largely preventable,[1] which underscores the need for caregivers in modern industrialized societies to be especially vigilant for environmental sources of lead that can cause illness in persons at high risk. Although the level of environmental exposure to lead is decreasing, toxic effects of lead remain the most common environmental illness among children in the United States. The report by Lin and colleagues in this issue of the *Journal*[2] compels us to revisit environmental exposure to lead from the perspective of a group that is newly understood to be at high risk — patients with chronic renal disease.

Increases in the body burden of lead can affect a variety of organ systems, including the kidneys. Acute lead poisoning should be distinguished from chronic lead poisoning. Patients with severe acute lead poisoning present with abdominal pain or "lead colic," cognitive deficits, peripheral neuropathy, arthralgias, decreased libido, a "lead line" at the junction of the teeth and gums, high blood levels (>80 μg per deciliter), and anemia with basophilic stippling on blood smears. Children, especially, are at risk for developmental and long-term cognitive deficits from lead poisoning. Although a child is considered to have lead poisoning when the blood lead level is higher than 10 μg per deciliter, current evidence suggests that there is no threshold blood level at which lead has no adverse effect on health. The priority must be identifying and removing the environmental source of lead. Current sources for this type of exposure are leaded paint and dust in old homes. Contamination of soil by emissions from leaded fuel also remains an important source of environmental lead, despite current laws against the use of leaded gasoline. The politics related to responsibility for this environmental contamination are complex. Inhabitants of our inner cities and persons who live at the edges of society's support networks are especially vulnerable.

Divalent lead compounds derived from environmental sources accumulate either rapidly or gradually and target proteins that bind to zinc or calcium at the molecular level.[3] For instance, erythrocytes store more than 99 percent of blood lead bound to the zinc-dependent delta-aminolevulinic acid dehydratase (ALAD). ALAD is an important enzyme in heme synthesis that is potently inhibited by lead, explaining tests that involve the measurement of porphyrin or the determination of heme-synthesizing enzyme activity.[4] However, measurement of blood lead levels and assessment of the rate of heme synthesis may not be helpful in diagnosing chronic lead poisoning. Long-term exposure to lead results in increases in the body lead burden that are not reflected in blood lead levels, because the lead content of red cells reflects only recent exposure. Approximately 90 to 95 percent of the lead is stored in

calcium-dependent skeletal pools with slow turnover, especially in cortical bone. More reliable techniques for measuring this bone lead content are x-ray fluorescence studies of bone and infusions of chelating agents followed by measurement of blood or urinary lead levels. Infusions of EDTA that extract lead from tissue are used both to diagnose and to treat increases in the body lead burden.

What is the relation between kidney disease and lead? In patients with acute toxic effects, lead accumulates in the proximal renal tubules. Clinical correlates of impaired tubular function in patients with acute toxic effects of lead are aminoaciduria and renal glucosuria due to diminished reabsorption and hyperuricemia due to diminished secretion of urate.[5] These acute effects are largely reversible by the cessation of exposure to lead, chelation therapy, or both. In contrast, ongoing exposure to lead over the course of many years results in progressive tubular atrophy and interstitial fibrosis. Animal models of chronic lead intoxication have revealed similar tubular findings and have highlighted the importance of disease in small and medium-sized arteries of the kidney.[6] The typical presentation of patients with chronic toxic effects of lead includes chronic renal insufficiency with a benign urinary sediment. Patients may also have hyperuricemia and hypertension. Such forms of acute or chronic renal injury are observed in patients with blatant elevations in blood lead levels or body lead burden (excretion of more than 600 μg of lead over the course of 72 hours after an EDTA-mobilization test).

What remains unclear is whether long-term exposure to low levels of environmental lead is clinically relevant to the kidney. Do mild increases in the body lead burden lead to renal disease? A number of population-based studies have noted associations between increased body lead burden and moderate declines in the glomerular filtration rate.[7,8,9] Such studies cannot tell us whether the increase in body lead burden is a cause or a consequence of chronic renal insufficiency. The latter is a distinct possibility. Renal insufficiency is known to prolong the time required to clear lead from blood, especially in people with long-term exposure to lead,[10] although this phenomenon has not been well studied.

Lin et al. present a comprehensive study that skillfully attempts to bridge the clinical gap between association and causality with regard to patients with a high-normal body lead burden.[2] There are two components to this work. A prospective, observational study was first conducted in a select group of patients with slowly progressive chronic renal insufficiency. Patients were assessed for factors known to influence the progression of renal disease. Multivariate analysis identified increased base-line body lead burden as a prognostic factor, yet one could argue that the absolute increase in relative risk is not clinically important. The investigators did not enroll patients identified at base line as having an overt elevation of body lead burden (excretion of more than 600 μg of lead over a period of 72 hours after an EDTA-mobilization test). After 24 months of observation, the body lead burden was assessed again. EDTA-mobilization tests identified 64 patients with a high-normal body lead burden (≥80 μg and <600 μg of urinary lead excretion over a 72-hour period) who then entered a 27-month intervention phase — a randomized, single-blind, placebo-controlled trial of EDTA-chelation therapy. Remarkably, glomerular filtration was significantly improved in patients who received chelation therapy as compared with patients given placebo. The authors argue that chelation therapy slows the progression of renal insufficiency in patients with a mildly elevated body lead burden.

An earlier and smaller study by the same group reached a similar conclusion.[11] Inexplicably, even though that study was a well-designed prospective trial, it has had a limited effect on the nephrology community. Very few clinics that treat progressive renal failure assess the body lead burden, even in patients with possible "saturnine gout." Critics argued that this small study was neither blinded nor

placebo-controlled. Clinicians may not have identified with the unique nature of the population under study (in Taiwan) or may have been dissuaded by historical caveats about EDTA toxicity.[12]

Will the current article change the practices of physicians in progressive-renal-failure clinics? The nephrology community may question whether this study relates to the population treated in their own clinics. It is not clear whether environmental lead contamination in Taiwan is quantitatively or qualitatively different from that in Europe or North America.[13] Perhaps the patients in the study were genetically susceptible to accumulation and toxic effects of lead. Studies of genetic associations suggest that alleles of the *ALAD* gene at chromosome 9q34 are among the molecular determinants of lead toxicity.[14] Moreover, genotype frequencies in this biallelic system vary globally.

Critics may argue that patients in the current study were not treated with angiotensin-converting–enzyme inhibitors if they did not have elevated blood pressure. The authors state that this practice reflected the accepted standard of care during the study period.[2] Other critics may argue that adverse effects of lead exposure can be exacerbated by EDTA therapy. Therefore, cognitive function may need to be evaluated in patients in future studies.

Finally, some may rightfully argue that the results do not demonstrate that lead-chelation therapy improves short-term renal function in humans. Rather, they show that EDTA-chelation therapy does. EDTA has protean biochemical and cellular effects both in vitro and in vivo. This known facet of EDTA precludes a definitive statement that chelation of lead is the important mechanism. Urinary lead content may be a surrogate index of EDTA efficacy. Yet, the most parsimonious model suggests that lead chelation is the explanation. At the minimum, let us acknowledge that this research group is to be commended for raising the awareness of physicians, governments, and patients about the importance of environmental exposure to lead as either a cause or a consequence of renal disease. That, in and of itself, represents a success.

Source Information

From St. Michael's Hospital, University of Toronto, Toronto.

References

1. Jacobs DE, Clickner RP, Zhou JY, et al. The prevalence of lead-based paint hazards in U.S. housing. Environ Health Perspect 2002;110:A599-A606.

2. Lin J-L, Lin-Tan D-T, Hsu K-H, Yu C-C. Environmental lead exposure and progression of chronic renal diseases in patients without diabetes. N Engl J Med 2003;348:277-286.

3. Godwin HA. The biological chemistry of lead. Curr Opin Chem Biol 2001;5:223-227.

4. Fontanellas A, Navarro S, Moran-Jimenez MJ, et al. Erythrocyte aminolevulinate dehydratase activity as a lead marker in patients with chronic renal failure. Am J Kidney Dis 2002;40:43-50.

5. Loghman-Adham M. Aminoaciduria and glycosuria following severe childhood lead poisoning. Pediatr Nephrol 1998;12:218-221.

6. Sanchez-Fructuoso AI, Blanco J, Cano M, et al. Experimental lead nephropathy: treatment with calcium disodium ethylenediaminetetraacetate. Am J Kidney Dis 2002;40:59-67.

7. Staessen JA, Lauwerys RR, Buchet J-P, et al. Impairment of renal function with increasing blood lead concentrations in the general population. N Engl J Med 1992;327:151-156.

8. Payton M, Hu H, Sparrow D, Weiss ST. Low-level lead exposure and renal function in the Normative Aging Study. Am J Epidemiol 1994;140:821-829.

9. Kim R, Rotnitsky A, Sparrow D, Weiss S, Wager C, Hu H. A longitudinal study of low-level lead exposure and impairment of renal function: the Normative Aging Study. JAMA 1996;275:1177-1181

10. Hryhorczuk DO, Rabinowitz MB, Hessl SM, et al. Elimination kinetics of blood lead in workers with chronic lead intoxication. Am J Ind Med 1985;8:33-42.

11. Lin JL, Ho HH, Yu CC. Chelation therapy for patients with elevated body lead burden and progressive renal insufficiency: a randomized, controlled trial. Ann Intern Med 1999;130:7-13.

12. Sanchez-Fructuoso AI, Prats D, Barrientos A. Treatment of chronic lead intoxication. Ann Intern Med 1999;131:716-716.

13. Yang T, Wu TN, Hsu SW, Lai CH, Ko KN, Liou SH. Blood lead levels of primary-school children in Penghu County, Taiwan: distribution and influencing factors. Int Arch Occup Environ Health 2002;75:528-534.

14. Kelada SN, Shelton E, Kaufmann RB, Khoury MJ. Delta-aminolevulinic acid dehydratase genotype and lead toxicity: a HuGE review. Am J Epidemiol 2001;154:1-13.

This article has been cited by other articles:

- Hollenberg, N. K. (2004). Lead Exposure and Chronic Renal Failure. *Arch Intern Med* 164: 2507-2507
- Yu, C.-C., Lin, J.-L., Lin-Tan, D.-T. (2004). Environmental Exposure to Lead and Progression of Chronic Renal Diseases: A Four-Year Prospective Longitudinal Study. *J Am Soc Nephrol* 15: 1016-1022
- Canfield, R. L., Henderson, C. R. Jr., Cory-Slechta, D. A., Cox, C., Jusko, T. A., Lanphear, B. P. (2003). Intellectual Impairment in Children with Blood Lead Concentrations below 10 {micro}g per Deciliter. *N Engl J Med* 348: 1517-1526
- (2003). Lead-Chelation Therapy -- A Treatment for Chronic Renal Disease?. *Journal Watch (General)* 2003: 1-1