Interaction of Blood Lead and δ-Aminolevulinic Acid Dehydratase Genotype on Markers of Heme Synthesis and Sperm Production in Lead Smelter Workers

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The gene that encodes δ-aminolevulinic acid dehydratase (ALAD) has a polymorphism that may modify lead toxicokinetics and ultimately influence individual susceptibility to lead poisoning. To evaluate the effect of the ALAD polymorphism on lead-mediated outcomes, a cross-sectional study of male employees from a lead–zinc smelter compared associations between blood lead concentration and markers of heme synthesis and semen quality with respect to ALAD genotype. Male employees were recruited via postal questionnaire to donate blood and urine for analysis of blood lead, zinc protoporphyrin (ZPP), urinary coproporphyrin (CPU), and ALAD genotype, and semen samples for semen analysis. Of the 134 workers who had ALAD genotypes completed, 114 (85%) were ALAD1-1 (ALAD1) and 20 (15%) were ALAD1-2 (ALAD2). The mean blood lead concentrations for ALAD1 and ALAD2 were 23.1 and 28.4 μg/dl (p = 0.08), respectively. ZPP/heme ratios were higher in ALAD1 workers (68.6 vs. 57.8 μmol/mol; p = 0.14), and the slope of the blood lead ZPP linear relationship was greater for ALAD1 (2.83 vs. 1.50, p = 0.06). No linear relationship between CPU and blood lead concentration was observed for either ALAD1 or ALAD2. The associations of blood lead concentration with ZPP, CPU, sperm count, and sperm concentration were more evident in workers with the ALAD1 genotype and blood lead concentrations ≥40 μg/dl. The ALAD genetic polymorphism appears to modify the association between blood lead concentration and ZPP. However, consistent modification of effects were not found for CPU, sperm count, or sperm concentration. *Key words*: δ-aminolevulinic acid dehydratase, coproporphyrin, genotype, lead, semen, smelters, zinc protoporphyrin. *Environ Health Perspect* 106:213–216 (1998). [Online 12 March 1998]
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Lead is recognized as a cause of secondary porphyria resulting from heme synthesis inhibition, characterized by elevated levels of blood δ-aminolevulinic acid (ALA) and zinc protoporphyrin (ZPP) and urinary ALA and coproporphyrin (CPU) (*1*). The biological effects of lead can be detected at blood lead concentrations below current U.S. occupational health protection standards, which require medical removal in cases of repeated blood lead concentrations exceeding 50 μg/dl or one blood lead concentration exceeding 60 μg/dl (*2*). Biological markers of heme synthesis inhibition can reveal the effects of lead at various stages in the heme synthesis pathway. Lead inhibits the second enzyme in the pathway, aminolevulinic acid dehydratase (ALAD), which synthesizes porphobilinogen from ALA (*3*). Decreased ALAD activity results in an increase of free ALA, the presence of which is postulated as one mechanism for the neurotoxic effects of lead (*4*). The action of lead at this point in the heme synthesis pathway is estimated by measuring the activity of ALAD in blood or the concentration of ALA in blood or urine. The formation of protoporphyrinogen IX from coproporphyrinogen III is inhibited by lead, resulting in an increase in CPU. Inactivation of coproporphyrinogen oxidase or impaired transport of coproporphyrinogen into mitochondria may underlie this effect (*5*). Lead also interferes with the chelation of iron into protoporphyrin IX to form heme. Whether the mechanism is due to ferrochetalase inhibition is unclear (*6*). Instead of heme, zinc protoporphyrin (ZPP) is formed. ZPP is considered a sensitive marker of lead exposure and is a commonly used marker of lead-induced heme synthesis inhibition.

The determinants of lead kinetics and individual susceptibility to lead toxicity in humans are not clearly defined, despite considerable experimental animal research. Interindividual variation in the effects of lead exposure is probably governed by a complex web of susceptibility that includes the type and route of exposure, nutritional status, gender, age, and genetic profile. A possible genetic component of variation in the bodily response to lead exposure is the gene that encodes ALAD.

ALAD is encoded by a single gene with two common alleles, ALAD1 and ALAD2, which are expressed as three distinct phenotypes: ALAD1-1, ALAD1-2, and ALAD2-2 (*7*). ALAD2, the less common variant, is prevalent in 10–20% of the Caucasian population (*7–11*). This polymorphism appears to modify the toxicokinetics of lead (*12,13*), and the presence of the ALAD2 allele has been associated with higher blood lead levels in lead-exposed workers and children (*11,14*). There are conflicting findings as to whether ALAD2 carriers are more susceptible to the ultimate health effects of environmental lead exposure. The ALAD2 genotype putatively enhances red cell binding of lead, which may increase blood lead burden and thus be viewed as harmful (*15*). Alternatively, the ALAD2 genotype may be associated with reduced lead deposition in other body compartments and may thus protect against systemic toxicity including impaired heme synthesis (*12*). This study describes the interaction of the effects of lead and the presence of the ALAD polymorphism on markers of heme synthesis and reproductive health in a population of male lead smelter workers.

Methods

This cross-sectional study was part of a larger study on the effects of occupational lead exposure on male reproductive health conducted at a lead–zinc smelter in Trail, British Columbia (*16*). Male employees of the smelter (n = 2,469) were recruited by postal questionnaire to participate in the study. Volunteers were solicited to donate

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semen, blood, and urine samples. The study protocol was approved by the University of Washington Human Subjects Committee, and informed consent for study participation was obtained from the volunteers. Venous blood samples were drawn by the company occupational health nurse into EDTA-containing tubes. The samples were refrigerated at 4°C until analyzed for blood lead and ZPP. Blood lead concentrations were measured using graphite furnace atomic absorption spectrophotometry (*17*). ZPP levels were ascertained by hematofluorometry (*18*) and reported as ZPP/heme ratios; residual blood samples were then stored at -20°C. ALAD genotype was determined for each worker for which a residual blood sample was available. Genotyping for ALAD was performed by the polymerase chain reaction method of Wetmur (*7*) with protocol modifications described by Smith et al. (*13*).

Spot morning-void urine samples were collected by the workers and delivered to the laboratory the day of or the day after the blood was drawn and were stored at -20°C until analyzed. Porphyrin profiles were assessed by HPLC-spectrofluorometric procedures (*19*). CPU was expressed as a concentration by volume (micrograms per liter) and by weight (micrograms per gram creatinine).

Semen samples were collected at home or on-site after a requested 48-hr period of abstinence from sexual activity and delivered to the field laboratory within 1 hr of collection. A complete semen analysis was performed according to the World Health Organization protocol (*20*). The results for sperm concentration and total sperm count, previously reported to be associated with blood lead concentration in this population (*16*), are presented here.

Data were initially explored using correlation analyses and scatter plots. Mean blood lead, ZPP/heme ratio, CPU, sperm count, and sperm concentration were compared by ALAD genotype. The relationships between blood lead concentration and markers of heme synthesis inhibition (ZPP and CPU) and sperm count and concentration were evaluated using multiple linear regression with separate models for each ALAD genotype and both genotypes combined (*21*). The slopes of the blood lead ZPP associations for the two genotypes were compared in a model with an interaction term for blood lead concentration and ALAD genotype. Age adjustment was performed in all models.

An additional analysis was conducted in reference to blood lead levels at or above regulatory action levels. Mean ZPP and CPU and geometric means of sperm count and sperm concentration were compared by genotype and blood lead concentration less than and greater than or equal to 40 µg/dl. This cutpoint was established based on an Occupational Safety and Health Administration worker health protection criterion that requires additional monitoring of any worker with a blood lead concentration >40 µg/dl. Removal from work is not required until the worker has repeated measures >50 µg/dl or a single measurement ≥60 µg/dl (*2*).

Results

Blood samples were donated by 152 workers (*16*), among whom there was sufficient residual sample to determine ALAD genotype for 134 workers. Porphyrin profiles could be determined for 119 of the genotyped workers. One hundred fourteen (85%) of the 134 workers were homozygous for the ALAD type 1 (ALAD1-1) and 20 (15%) were heterozygous (ALAD1-2) (Table 1). No workers were homozygous for the type 2 allele. Compared to workers with ALAD2, workers with ALAD1 were slightly older (mean age 40.1 vs. 39.0 years) and had slightly longer average tenure (17.5 vs. 15.8 years), but fewer years in the higher lead exposure areas of the smelter (4.3 vs. 4.7). Semen samples were available for 106 workers among those for whom ALAD genotyping was completed: 89 were ALAD1 and 17 were ALAD2. The mean blood lead concentration of workers with ALAD2 was greater than those with ALAD1 (28.4 vs. 23.1 µg/dl, $p = 0.08$). In contrast, the ZPP/heme ratios were lower for workers with the ALAD2 genotype (57.8 vs. 68.6 µmol/mol, $p = 0.14$). Differences in geometric mean sperm count and concentration were minimal.

The linear associations between blood lead, ZPP, and ALAD genotype are displayed in Table 2 and Figures 1 and 2. As expected, blood lead concentration was strongly predictive of ZPP ($R^2 = 0.47$). The relationship between blood lead and ZPP appeared to be modified by ALAD genotype. The slope of this relationship for ALAD1 workers was 2.83 ($p<0.0001$), compared to 1.50 ($p = 0.0004$) for ALAD2 workers. The coefficient for the interaction of ALAD genotype and blood lead level on ZPP was 1.30 ($p = 0.06$). Urinary coproporphyrin excretion did not vary by blood lead concentration on a linear scale for either genotype ($R^2<0.03$ for all models). The log values of total sperm count and sperm concentration were inversely correlated with blood lead concentration (p = 0.02 and 0.10, respectively), but this association did not vary by ALAD genotype.

Differences for ZPP and CPU levels by ALAD genotype were evident when workers with blood lead levels below and greater than or equal to 40 µg/dl were compared (Table 3). These differences were more pronounced at or above 40 µg/dl. Mean CPU concentration for ALAD1-1 was

Table 1. Distribution of age, blood lead concentration, indicators of heme synthesis, and sperm count and concentration by δ-aminolevulinic acid dehydratase (ALAD) genotype in lead smelter workers

	ALAD1-1 ($n = 114$)	ALAD1-2 ($n = 20$)	
	Mean ± SD	Mean ± SD	p-Value
Age	40.1 ± 7.1	39.0 ± 7.8	0.58
Blood lead (µg/dl)	23.1 ± 12.2	28.4 ± 11.7	0.08
ZPP (µmol/mol heme)	68.6 ± 48.0	57.8 ± 24.4	0.14
Coproporphyrin	47.4 ± 41.6	41.6 ± 36.8	0.59
Creatinine-adjusted coproporphyrin	20.8 ± 19.5	19.3 ± 15.7	0.76
Sperm concentration	60.3 ± 3.3[a]	60.3 ± 2.1[a]	0.96
Total sperm count	134 ± 3.7[a]	148 ± 2.5[a]	0.91

SD, standard deviation.
[a]Geometric mean and geometric SD.

Table 2. Linear regression models of zinc protoporphyrin regressed on blood lead concentration by δ-aminolevulinic acid dehydratase (ALAD)

Model	n	Variables[a]	β	p-Value	R^2
Combined	134	Blood lead	2.53	<0.0001	0.47
		Age	0.76	0.07	
ALAD1-1	114	Blood lead	2.83	<0.0001	0.52
		Age	0.96	0.04	
ALAD1-2	20	Blood lead	1.50	0.0004	0.57
		Age	-0.74	0.18	
Interaction	134	Blood lead	1.53	0.02	0.52
		Age	0.68	0.09	
		ALAD	-11.59	0.58	
		ALAD*Blood lead	1.30	0.06	

[a]Variable coding: ALAD: ALAD1 = 1, ALAD2 = 0; blood lead concentration = µg/dl; zinc protoporphyrin = µmol/mol heme; age = years.

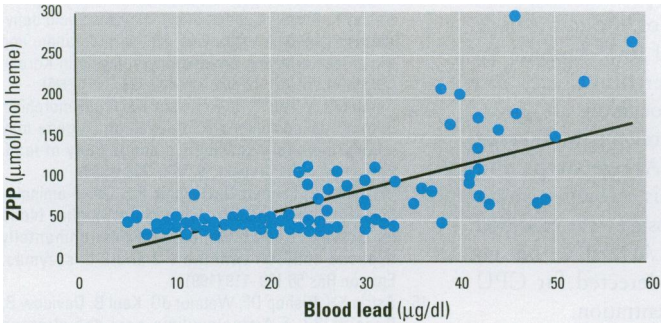

Figure 1. Zinc protoporphyrin (ZPP) level by current blood lead concentration for workers with ALAD1-1 genotype.

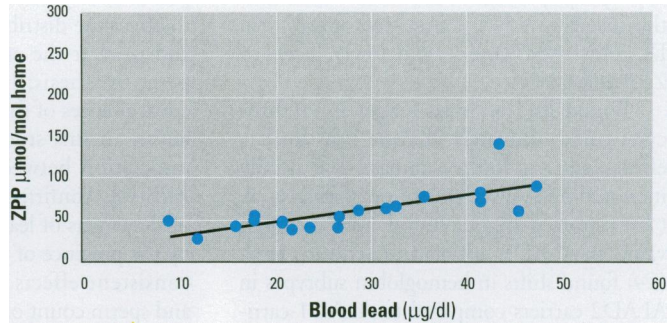

Figure 2. Zinc protoporphyrin (ZPP) level by current blood lead concentration for workers with ALAD1-2 genotype.

threefold greater than for ALAD1-2 (46.5 vs. 13.6 µg/l). A similar association, albeit attenuated, was seen for the creatinine-adjusted CPU. CPU did not, however, increase with increasing blood lead concentration as would be expected. The effect of blood lead concentrations >40 µg/dl on total sperm count and sperm concentration were most apparent in workers with the ALAD type 1 genotype. The geometric mean sperm count and concentration values for ALAD1 workers in this blood lead range were approximately half those with ALAD type 2 genotype. These results, however, are not statistically significant, as they are based on only four workers with ALAD2 and a blood lead concentration >40 µg/dl.

Table 3. Zinc protoporphyrin, coproporphyrin, sperm count, and sperm concentration by δ-aminolevulinic acid dehydratase (ALAD) genotype and blood lead concentration above and below 40 µg/dl

		ALAD1-1		ALAD1-2		
	Blood lead (µg/dl)	*n*	Mean ± SD	*n*	Mean ± SD	*p*-Value
Zinc protoporphyrin	<40	98	55.7 ± 27.1	15	48.5 ± 12.5	0.10
(µmol/mol heme)	≥40	16	147.3 ± 70.3	5	85.6 ± 31.5	0.03
Coproporphyrin	<40	90	47.5 ± 42.9	13	50.3 ± 38.1	0.81
(µg/l)	≥40	12	46.5 ± 31.6	4	13.6 ± 7.8	0.01
Creatinine-adjusted	<40	90	21.2 ± 20.1	13	22.9 ± 15.9	0.76
coproporphyrin (µg/g)	≥40	12	18.4 ± 14.0	4	7.5 ± 7.2	0.16
Sperm concentration	<40	82	63.6 (2.9)[a]	13	61.1 (2.2)[a]	0.89
(million sperm/ml)	≥40	7	32.2 (7.4)[a]	4	61.8 (1.9)[a]	0.54
Total sperm count	<40	82	152 (3.4)[a]	13	155 (3.4)[a]	0.95
(million sperm)	≥40	7	58 (10.0)[a]	4	116 (3.0)[a]	0.59

SD, standard deviation.
[a]Geometric mean (geometric SD).

Discussion

The association of blood lead concentration and ZPP was modified by ALAD genotype in this population of male lead smelter workers. Despite having lower blood lead concentrations, workers with the ALAD1 genotype had, on average, higher ZPP levels compared to those with ALAD2. This difference was most pronounced at blood lead levels >40 µg/dl.

The nonrandom method of worker recruitment, the study sample size, and the absence of female workers were the primary limitations of this cross-sectional study. The smelter workers volunteered to participate by donating a blood sample following recruitment via a mailed questionnaire. The participation rate was low, in large part due to the semen sample donation requirement of the original study; nevertheless, the volunteers were similar to the overall population with respect to age, length of employment, work area, and blood-lead monitoring history (*16*). It is unlikely that ALAD genotype played a role in a worker's decision to participate. The prevalence of the ALAD1-2 allele was in the expected range of 10–20% (*7–11*). The small number of workers with the variant allele represented a sparse distribution of blood lead concentrations, with few exceeding 40 µg/dl. The statistical power of the study to model the exposure–gene interaction was limited accordingly. The absence of female workers limits the generalizability of these data particularly insofar as gender may modify the effects of lead on heme synthesis (*22*).

The ALAD polymorphism appears to influence the toxicokinetics of lead. However, the evidence of either allele predisposing an individual to the adverse health effects of lead is inconclusive. In the current study mean blood lead levels of workers with the ALAD2 genotype were somewhat higher than those with ALAD1. Similar observations have been made of occupationally exposed adults and environmentally exposed children (*11,12,14*). Despite the higher blood lead concentrations, the association between blood lead and ZPP levels of ALAD2 workers was attenuated. This phenomenon was also reported in a study of Korean storage-battery-manufacturing workers where a subgroup of workers with the highest lead exposures had lower ZPP concentrations when the ALAD2 genotype was present (*12*).

Suggestive of a similar mechanism, CPU concentrations were lower in workers with the ALAD2 allele when blood lead levels exceeded 40 µg/dl. However, this observation may be an artifact because the overall CPU concentration was not associated with blood lead concentration. Intraindividual variation of urinary coproporphyrin concentration, especially measured in spot samples, can be large (*1*), which limits its utility as a biomarker of heme synthesis toxicity. The semen quality parameters of total sperm count and sperm concentration were also suggestive of a possible protective effect of ALAD2 genotype for workers with blood lead levels ≥40 µg/dl. Although these differences were based on too few individuals to be statistically stable, they do contribute evidence that the ALAD polymorphism may modify the health effects of lead.

A mechanism for the modified associations between blood lead and ZPP by ALAD genotype has not been clearly established. It has been hypothesized that the variant form of ALAD (ALAD2) may bind lead more tightly than ALAD1 and make it less bioavailable (*23*). Should this be the case, given constant exposure, less lead would be bioavailable for inhibition of heme synthesis downstream of ALAD in this biochemical pathway. The result of this enhanced protein binding of lead in ALAD2 carriers would be a decrease in the amount of bioavailable lead to inactivate

coproporphyrinogen oxidase or to inhibit the insertion of iron into protoporphyrin IX. This then would yield lower levels of ZPP and CPU.

Bound lead retained longer in erythrocytes could ultimately increase risks for late effects, such as kidney damage and mildly increased hemoglobin turnover. Smith et al. (*13*) reported higher blood urea nitrogen values in ALAD2 carriers and Schwartz et al. (*24*) found shifts in hemoglobin subtypes in ALAD2 carriers compared to ALAD1 carriers. This theory is also supported by apparent differential partitioning by ALAD genotype of lead in bone of carpenters with low blood lead levels (*13*). The theoretical differential binding of lead by the ALAD isozymes does not indicate greater susceptibility to lead for persons with the ALAD2 genotype. In the current study, apparent inhibition of heme synthesis (elevated ZPP) was more pronounced in workers with the ALAD1 genotype, suggesting that they, rather than the workers with ALAD2 and greater blood lead concentrations, are predisposed to the adverse hematologic effects of lead. The neurological effects of lead may be similarly altered. An elevated concentration of plasma ALA was shown to be higher in battery workers with homozygous ALAD1 genotype compared to heterozygous ALAD1-2 workers (*25*). This effect was independent of blood lead concentration and age. To the extent that the increased ALA concentration contributes to the neurological effects of lead, persons with homozygous ALA1 genotype may be more susceptible to the neurological effects of lead. Though based on few cases, adolescents with the ALAD2 genotype scored higher than those with ALAD1 on a battery of neuropsychological tests (*26*). Conversely, ALAD2 carriers with low blood lead concentrations showed more evidence of impaired renal function (*13*).

The role of the ALAD genetic polymorphism in conferring susceptibility to the adverse health outcomes associated with lead exposure has yet to be clearly defined. The presence of the ALAD type 2 allele appears to affect the distribution of lead in the body and to alter the effect of lead exposure on heme synthesis; however, the causes and consequences of these associations are speculative. In this study a previously observed association between ALAD genotype and ZPP was confirmed. This sensitive marker of the effects of lead exposure was modified by the presence of the ALAD2 allele, but no consistent effects were detected for CPU and sperm count or concentration.

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