The Protective Effect of δ-Aminolevulinic Acid Dehydratase 1-2 and 2-2 Isozymes against Blood Lead with Higher Hematologic Parameters

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Previous studies have suggested that δ-aminolevulinic acid dehydratase (ALAD) types 1-2 or 2-2 are protective against the toxicity of blood lead (PbB) when zinc protoporphyrin (ZPP) levels are low because of differential binding of lead in erythrocytes. The hypothesis is that subjects with the *ALAD 1-1* genotype are more susceptible to lead exposure with impaired hematologic synthesis and therefore that iron nutrition is more important in those with the *ALAD 1-1* genotype. The purpose of this study was to prove the protective effect of ALAD 1-2/2-2 against PbB with higher hematologic parameters. Data on 1,219 male workers from eight lead-using factories in the Republic of Korea were examined in this cross-sectional study. Blood samples were evaluated for PbB, ZPP, hemoglobin (Hb), and serum iron (SFe) concentrations and *ALAD* genotypes. The overall prevalence of the *ALAD 1-2/2-2* genotype was 9.3%, which was associated with lower log ZPP ($p < 0.001$) and higher Hb ($p = 0.014$) levels. For the subjects with normal iron status (SFe levels > 60 μg/dL), those with the *ALAD 1-1* genotype were more likely to be anemic (adjusted odds ratio of 5.2; 95% confidence interval, 1.2–22.6) than those with *ALAD 1-2/2-2*. The study confirms the protective effects of *ALAD 1-2/2-2* polymorphisms against PbB on hematologic pathways. In order to promote health and to minimize the toxicity of lead exposure more effectively, the nutritional management of iron in Korean workers should take both their *ALAD* genotypes and occupational lead exposures into account. *Key words:* δ-aminolevulinic acid dehydratase polymorphism, hemoglobin, lead, zinc protoporphyrin. *Environ Health Perspect* 112:538–541 (2004). doi:10.1289/ehp.6464 available via *http://dx.doi.org/* [Online 9 December 2003]

Some workers are exposed to high environmental lead levels in modern society. The control of lead exposure by legislation and modern technology is undoubtedly responsible for the reduction in acute lead poisoning over the past few decades in Korea (Lee 1992). Despite these declines, there is still considerable concern regarding the toxicologic implications of lead exposure and the subtle health effects at blood lead (PbB) levels around 30 μg/dL in Korean lead workers with a significantly higher prevalence of iron deficiency (Kim et al. 2003).

There is a considerable interindividual variation in the toxicokinetics of lead (Fleming et al. 1998; Goering and Fowler 1987; Schwartz et al. 1995; Smith et al. 1995; Wetmur et al. 1991b). Lead inhibits three enzymes—aminolevulinic acid dehydratase (ALAD), coporphyrinogen oxidase, and ferrochelatase—in the heme-synthesis pathway, with its effects on ALAD being most profound (Onalaja and Claudio 2000). The *ALAD* polymorphism codes for one of three isozymes (termed ALAD 1-1, ALAD 1-2, and ALAD 2-2) and has been reported to account for significant variation in intravascular and soft-tissue binding and in the long-term deposition of lead (Kelada et al. 2001). The *ALAD 2* allele has been shown to modify the toxicokinetics of lead by coding for a more electronegative enzyme that may bind positively charged lead ions more tightly than does the ALAD-1 protein (Wetmur 1994; Wetmur et al. 1991a). PbB concentrations are reportedly higher in subjects carrying the *ALAD-2* allele than in subjects with the ALAD 1-1 isozyme (Fleming et al. 1998; Wetmur 1994; Wetmur et al. 1991a, 1991b; Ziemsen et al. 1986). However, several other studies (Bergdahl et al. 1997; Hu et al. 2001; Schwartz et al. 1995; Smith et al. 1995) have reported no association between *ALAD* genotypes and PbB levels. The results of the studies of Smith et al. (1995) and Hu et al. (2001) suggest that ALAD modifies PbB and/or the toxicokinetics of lead only in those with a high body lead burden. Recent studies into occupational lead exposures support the hypothesis that the protective effect of the variant allele is due to the binding of lead and maintaining it in the intravascular space in a less bioavailable form with lowered zinc protoporphyrin (ZPP) levels, a parameter of the hematologic toxic consequences of lead (Fleming et al. 1998; Schwartz et al. 1997, 2000; Sithisarankul et al. 1997).

Hypotheses concerning lower ZPP levels even in the presence of higher concentrations of PbB and the ALAD 1-2 or 2-2 isotype question whether ALAD mediates the levels of hematologic parameters. The prevalence of the *ALAD-2* allele varies with race and ethnicity. For example, it has been reported that only 9.9% of Koreans carry the allele (Lee et al. 2001), whereas approximately 20% of Caucasians have the allele (Onalaja and Claudio 2000; Wetmur et al. 1991b; Ziemsen et al. 1986). With increased attention being paid to nutrition as a secondary means of mitigating the effects of occupational and environmental exposure to lead (Cheng et al. 1998; Mahaffey 1990), improved iron nutrition has been found to be important to the reduction of the toxicity of PbB (Mahaffey 1995). One of the most prevalent nutritional concerns among Korean lead workers has been a higher prevalence of iron deficiency compared with the general population, although the prevalence of anemia in the overall Korean male population is no longer of serious concern.The recent study of Kim et al. (2003) showed that 42% of lead workers have low iron store status compared with only 21% of control subjects. For both populations, the prevalence of anemia determined by a hemoglobin (Hb) level < 13.5 g/dL was very low (13% lead workers vs. 0% control), and the mean Hb level was 14.7 g/dL. This study also indicated that the dietary iron intake was inversely associated with ZPP. If the *ALAD* genotype modifies hematologic parameters to reduce ZPP even in the presence of higher PbB, nutritional management strategies for secondary preventive intervention against lead toxicity should vary with *ALAD* genotype. Here we report a cross-sectional evaluation of differences of hematologic parameters by *ALAD* genotype in 1,219 male lead workers from Korea.

Materials and Methods

Study population. Participation in the study was voluntary, and all participants provided written, informed consent. The study protocol was approved by the Institutional Review Board of the College of Medicine, Soonchunhyang University.

Employees from eight lead-using factories [five storage-battery factories, two secondary-smelting factories, and one litharge (PbO) making factory] were studied. Storage-battery factories manufacture batteries for cars and trucks, large industrial batteries, and/or smaller batteries for consumer products. All of the workers included in the study were male, and they were either lead workers who were

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directly engaged in lead-using operations or nonlead workers who were engaged in administrative or clerical jobs at the same eight factories. Both lead and nonlead workers were screened at a mandatory semi-annual health surveillance program that included environmental and biologic monitoring (e.g., levels of PbB, ZPP, and Hb) and liver and renal function examinations by the Institute of Industrial Medicine, Soonchunhyang University. Workers without any detectable medical problems were considered eligible subjects for the present study. Out of a total of 1,287 male workers, the eligible study participants consisted of 1,074 lead workers (88%) and 145 nonlead workers (12%), with a mean age of 35.8 years (range, 19–72 years). The mean employment duration of lead workers was 6.7 years (range, 0–27 years), and that of nonlead workers was 5.9 years (range, 0–20 years).

Study variables. *ALAD* genotype, PbB, and Hb levels were determined in EDTA-treated whole-blood specimens obtained during medical surveillance in autumn 2000 at Soonchunhyang University. A modified polymerase chain reaction (PCR)-based protocol was used for *ALAD* genotyping (Wetmur et al. 1991a, 1991b), performed sequentially and in duplicate on 0.5 μL whole blood using nested primers. Detailed descriptions of the *ALAD* genotyping methods are available elsewhere (Lee et al. 2001). PbB was measured in duplicate with a Zeeman background-corrected atomic absorption spectrophotometer (model Z-8100; Hitachi, Tokyo, Japan) using the standard addition method of the National Institute of Occupational Safety and Health (Kneip and Crable 1988) at the Institute of Industrial Medicine, Soonchunhyang University, which is a certified reference laboratory for lead measurement in Korea. ZPP levels were measured by a portable hematofluorometer (Aviv-206; Aviv, Lakewood, NJ, USA) at the medical surveillance sites (Blumberg et al. 1977). Hb was assayed by the cyanmethemoglobin method (model Ac-T; Beckman Coulter, Fullerton, CA, USA). Serum iron (SFe) levels were measured by spectrophotometry (TBA-40FR biochemical analyzer; Hitachi, Tokyo, Japan).

Data analysis. The primary goals of the analysis were to examine relations of the *ALAD* genotypes with hematologic parameters (blood ZPP and Hb), PbB, and SFe while controlling for covariates, and to evaluate whether the *ALAD* genotype modified relations with PbB or SFe on above relations.

Statistical analyses were performed using SAS, version 8.12 (SAS Institute, Cary, NC, USA). Detailed frequency distributions and summary statistics were examined for all study variables. Relations between variables were assessed by correlations and multiple linear regressions for continuous outcome data, and multiple logistic regression for dichotomous outcomes. These analyses were conducted on data from all workers in both direct lead-using and nonlead-using environments in the same factories because the PbB levels of nonlead workers in the study were significantly higher than the mean PbB level of the general Korean population (0.24 μmol/L, 5 μg/dL) (Kim et al. 2001).

Covariates examined in linear regression and logistic regression models comprised age, employment duration, body mass index (BMI), and alcohol and tobacco consumption. Covariates were retained in the final regression and logistic models if they were significant predictors of hematologic parameters. We transformed ZPP values to a logarithmic scale to account for the skewness of the ZPP distribution. Multiple linear regression was used to examine the association between ALAD and log ZPP or Hb concentration after controlling for PbB, SFe, and other covariates. To evaluate the effect of modification by ALAD, we added cross-product terms of ALAD × PbB and ALAD × SFe to the models of log ZPP and Hb (one cross-product at a time).

Crude and adjusted odds ratios (ORs) were calculated using logistic regression to identify predictors of anemia (Hb levels < 13.5 g/dL) from the *ALAD* genotype among all workers, controlling covariates. Given that the *ALAD* genotype appears to modify lead toxicokinetics and that SFe is a source of iron in the biosynthesis pathway of Hb, we hypothesized that both *ALAD* genotype and iron status are selection factors for special nutrition care for the prevention of anemia. To evaluate the relations of SFe with ALAD and Hb, we calculated crude and adjusted OR of the *ALAD* genotypes, dichotomous iron status (normal and deficient), and anemic status (normal and anemic) using logistic regression analysis. A deficient iron status was defined as SFe levels < 10.74 μmol/L (60 μg/dL), which is a recognized cutoff value for iron-deficient erythropoiesis (Gibson 1990).

Results

Descriptive results. Lead workers exhibited a higher mean PbB level and a higher mean ZPP level than nonlead workers (Table 1). The majority of both lead and nonlead workers currently consumed both tobacco and

Table 1. Characteristics of study subjects.

Variables	Lead workers (*n* = 1,074)	Nonlead workers (*n* = 145)
Age (years)	35.4 ± 8.1 (19.0–70.0)	36.1 ± 7.6 (20.0–72.0)
Employment duration (years)	6.7 ± 4.6 (0.0–27.0)	5.9 ± 4.5 (0.0–20.0)
BMI	22.7 ± 2.7 (16.5–34.4)	23.6 ± 2.7 (17.4–32.7)
PbB		
μmol/L	1.25 ± 0.66 (0.19–4.06)	0.45 ± 0.14** (0.17–0.80)
μg/dL	26.0 ± 13.7 (4.0–84.6)	9.4 ± 3.0** (3.5–16.6)
ZPP		
μmol/mol heme	71.1 ± 51.1 (32.2–620.2)	53.3 ± 10.0* (32.2–79.8)
μg/dL	50.8 ± 36.5 (23.0–443.0)	38.0 ± 7.1* (23.0–57.0)
Hb (g/dL)	14.7 ± 0.9 (10.1–17.7)	14.9 ± 0.9 (12.1–17.8)
SFe (μmol/L)	20.2 ± 7.7 (4.1–85.4)	20.0 ± 8.6 (6.8–64.1)
Smoking [*n* (%)]		
Current	786 (73.2)	96 (66.2)
Never smoked or ex-smoker	288 (26.8)	49 (33.8)
Alcohol consumption [*n* (%)]		
Current	824 (76.7)	114 (78.6)
Never or no longer	250 (23.2)	31 (21.4)
ALAD genotype [*n* (%)]		
1-1	971 (90.4)	135 (93.1)
1-2 or 2-2	103 (9.6)	10 (6.9)

Values shown are mean ± SD (range).
*$p < 0.05$; **$p < 0.01$.

Table 2. Lead biomarker variables and hematologic indices by *ALAD* gene status.

Variables	*ALAD 1-1* (*n* = 1,106)	*ALAD 1-2/2-2* (*n* = 113)
Age (years)	35.5 ± 8.0 (20.0–72.0)	35.6 ± 8.0 (19.0–63.0)
Employment duration (years)	6.6 ± 4.6 (0.0–27.0)	6.8 ± 4.6 (0.0–20.0)
BMI	22.9 ± 2.8 (16.7–34.4)	22.7 ± 2.4 (16.5–28.0)
PbB		
μmol/L	1.15 ± 0.67 (0.17–4.66)	1.23 ± 0.66 (0.19–3.18)
μg/dL	23.9 ± 14.0 (3.5–84.6)	25.6 ± 13.7 (3.9–66.3)
ZPP		
μmol/mol heme	69.9 ± 50.2 (32.2–620.2)	60.5 ± 23.3 (32.2–161.0)
μg/dL	49.9 ± 35.8 (23.0–443.0)	43.2 ± 16.6 (23.0–115.0)
Hb (g/dL)	14.7 ± 0.9 (10.1–17.8)	14.9 ± 0.8 (12.3–17.2)
SFe (μmol/L)	20.2 ± 7.9 (4.12–85.38)	20.6 ± 7.2 (9.0–41.5)

Values shown are mean ± SD (range).

alcohol. Ninety percent of both types of workers were homozygous for the *ALAD 1-1* genotype (Table 1). Age, duration of job, BMI, and Hb and SFe levels did not vary with *ALAD* genotype (Table 2). There were also no significant differences in PbB and ZPP levels by *ALAD* genotype.

Correlation of variables and associations with ALAD genotype. Table 3 lists the unadjusted correlations of study variables. As expected, PbB concentrations were strongly positively correlated with log ZPP ($r = 0.689$) and negatively correlated with Hb ($r = –0.195$). Log ZPP values were also negatively correlated with Hb ($r = –0.313$) and showed a very weak negative correlation with SFe ($r = –0.059$, $p < 0.05$).

In multiple linear regression models, *ALAD* genotype was associated with log ZPP (Table 4, model 1). The results of Hb (model 2) with *ALAD* genotype showed that subjects with ALAD 1-2 or 2-2 isozymes had significantly ($p < 0.05$) higher Hb levels when PbB and SFe levels and other confounding covariates (age, employment duration, BMI, alcohol consumption, and cigarette smoking) were controlled. There were no significant interactions of *ALAD* genotype with PbB or SFe (data not shown). The hypothesis that *ALAD* genotype modifies hematologic parameters was confirmed: the mean Hb level was 0.22 g/dL higher in subjects with the *ALAD-2* allele. Subjects with the *ALAD 1-1* allele with a higher amount of bioavailable lead showed exacerbated hematologic toxicity with similar PbB and SFe levels.

Predictors of anemia. The logistics regression model showed that the *ALAD* genotype was associated with the presence of anemia (Table 5). After dichotomizing anemic and normal ranges of Hb at 13.5 g/dL (Gibson 1990), persons with *ALAD 1-1* were more likely to have anemia [crude OR = 3.4; 95% confidence interval (95% CI), 1.2–13.5]. These associations were also observed after controlling for age, employment duration, BMI, alcohol consumption, and cigarette smoking. The interaction of ALAD with SFe was analyzed to examine whether the *ALAD* genotype moderates the effect of iron status; no interaction was observed (data not shown). The analysis was further conducted with grouped subjects by their iron-deficient erythropoietic status as determined by SFe levels < 10.74 µmol/L (60 µg/dL) (Gibson 1990). As expected, individuals with iron-deficient erythropoietic status were more likely to have anemia, with an adjusted OR of 3.5 (95% CI, 1.7–7.0; data not shown). Moreover, when subjects with the *ALAD 1-1* genotype were also iron deficient ($n = 65$), their probability of being anemic was 11.8-fold higher than that of subjects with *ALAD 1-2*/*2-2* genotypes and normal iron status (95% CI, 2.3–58.6). When subjects with normal iron status were compared, individuals with the *ALAD 1-1* genotype were 5.2-fold more likely to be anemic than were individuals with the *ALAD-2* allele (95% CI, 1.2–22.6). Comparison among subjects with iron-deficient status by *ALAD* genotypes was not possible because only one subject had both the *ALAD-2* allele and anemia.

Table 3. Correlation analysis of study variables.[a]

	Age	Employment duration	BMI	PbB	Log ZPP	Hb
Employment duration	0.50***					
BMI	0.10**	0.12***				
PbB	0.35***	0.18***	–0.05			
Log ZPP	0.34***	0.13***	–0.03	0.69***		
Hb	–0.22***	–0.03	0.22***	–0.20***	–0.31***	
SFe	0.01	0.04	–0.01	–0.00	–0.06*	0.16***

[a]Unadjusted Pearson's correlation for all subjects. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

Table 4. Multiple linear regression models of log ZPP (model 1) and Hb (model 2) with SFe, PbB, and *ALAD* genotype.[a]

	Estimate	SE	*t*-Statistic	No.	R^2
Model 1: log ZPP with *ALAD*					
Intercept	3.63	0.08	45.23***	1,219	0.50
SFe (µmol/L)	–0.003	0.001	–2.40*		
PbB (µmol/L)	0.39	0.01	30.10***		
ALAD 1-2/2-2	–0.11	0.03	–4.03*		
Model 2: Hb with *ALAD*					
Intercept	133.13	2.55	52.19***	1,219	0.16
SFe (µmol/L)	0.19	0.03	5.78***		
PbB (µmol/L)	–1.67	0.41	–4.11***		
ALAD 1-2/2-2	2.16	0.88	2.46*		

[a]In addition to variables listed under each model, models also controlled for age, employment duration, alcohol consumption, and cigarette smoking for all subjects. *$p < 0.05$. ***$p < 0.001$.

Table 5. Association between dichotomous outcome variables of hemoglobin with *ALAD* genotype and SFe status.[a]

ALAD genotype	Iron status[b]	Hb		Total	Crude OR (95% CI)	Adjusted OR (95% CI)[d]
		Normal	Anemic[c]			
1-2/2-2	—	110 (97%)	3 (3%)	113	1.0	1.0
1-1	—	1,013 (91%)	93 (9%)	1,106	3.4 (1.2–13.5)	4.1 (1.0–13.7)
Total	—	1,123	96	1,219		
1-2/2-2	Normal	105 (98%)	2 (2%)	107	1.0	1.0
1-1	Normal	962 (92%)	79 (8%)	1,041	4.3 (1.3–26.4)	5.2 (1.2–22.6)
1-2/2-2	Deficient	5 (83%)	1 (17%)	6	10.5 (0.4–130.1)	13.2 (0.5–348.0)
1-1	Deficient	51 (78%)	14 (22%)	65	14.4 (3.8–93.9)	11.8 (2.3–58.6)
Total		1,123	96	1,219		

[a]Logistic regression models for all subjects. [b]Cutoff value for iron-deficiency: SFe level = 10.74 µmol/L (60 µg/dL). [c]Cut-off value for anemia: Hb level = 13.5 g/dL. [d]Adjusted for age, employment duration, BMI, alcohol consumption, and cigarette smoking.

Discussion

The decline in PbB levels among Korean lead workers over the past few decades reflects primary interventions including legislation on adequate industrial hygiene practices, improved work environments, and mandatory health surveillance. Nonetheless, considerable concern remains regarding lead levels, and proper nutrition has been recognized as an adjunct to the reduction of occupational lead exposure by altering susceptibility to lead toxicity. In addition, studies using genetic markers of susceptibility to environmental toxicants have suggested that certain genes can make individuals more vulnerable to environmental toxins such as lead. The present study focused on the relationship between different *ALAD* genotypes and differentiated lead-induced impairment of hematopoiesis, as an aid to seeking appropriate nutritional strategies to counteract the hematologic toxicity of lead exposure.

Data from male Korean lead workers with similar PbB and SFe concentrations, durations of employment in lead industry, BMIs, and ages suggest that the *ALAD* genotype influences levels of ZPP and Hb and, consequently, the prevalence of anemia. Subjects with the *ALAD 1-2* or *2-2* genotype showed significantly lower log ZPP and higher Hb levels compared with *ALAD 1-1* individuals (Table 4). This analysis was conducted to evaluate whether *ALAD* genotype modified the relation between lead exposure and Hb synthesis with differentiated ZPP levels (log ZPP).

ZPP levels, derived from the substrate (protoporphyrin IX) of the last enzyme in the heme-synthesis system (ferrochelatase), should only be increased by the presence of bioavailable lead; PbB that is strongly bound by an ALAD isozyme, for example, should not inhibit ferrochelatase. Therefore, lead binding by ALAD isozymes with different affinities differentially limits its bioavailability (Schwartz et al. 1995). We hypothesized that the different bioavailability of PbB determined by ALAD isotypes differentially affects ferrochelatase activity and therefore Hb synthesis. Our data involving different Hb concentrations of different ALAD isotypes confirmed this hypothesis.

Furthermore, the prevalence of anemia in subjects with ALAD 1-2/2-2 isotypes was significantly lower than in subjects homozygous for *ALAD 1-1* (Table 5). Anemia is a late sign in industrial lead poisoning, and in the past it was severe among subjects exposed to lead (Mahaffey 1995). However, recent data indicate that anemia is less intense and less common in Korean lead workers than previously thought, although impaired iron status has been reported in this population (Kim et al. 2003). Lead intoxication impairs iron use and produces a hemolytic tendency, both of which complicate the mechanism of anemia (Albahary 1972). As mentioned above, the two target sites in the biosynthetic pathway of heme by PbB are the sites of activity of ALAD and ferrochelatase (Moore and Goldberg 1985). Lead is also known to interfere with the mitochondrial energy metabolism that is necessary to reduce ferric iron to ferrous iron before the insertion of iron into the porphyrin ring. Therefore, protoporphyrin accumulates when there is insufficient ferrous iron for its incorporation by ferrochelatase into heme (Mahaffey 1990). Ferrochelatase activity is sensitive to both lead and iron. Kapoor et al. (1984) reported that the enzyme kinetics of ferrochelatase in isolated human reticulocytes changes with both iron and lead concentrations. Ferrochelatase is more sensitive to lead effects when iron deficiency is present. Our data provide evidence that the *ALAD* genotype modifies both the toxicokinetics of lead in the hematologic pathway and the prevalence of anemia in lead exposure. In addition, our findings suggest that with impaired iron status and the presence of the *ALAD 1-1* genotype, reduction of heme synthesis causes higher incidences of anemia when PbB levels are controlled (Table 5). These data imply that subjects with *ALAD 1-2* or *2-2* are better able to use iron for Hb synthesis. Therefore, the impaired iron nutrition of individuals with the *ALAD 1-1* isozyme will make them more susceptible to the toxic effects of lead in heme biosynthesis than subjects with other ALAD isozymes. Because the prevalence of anemia can be modified by iron status, it is important to reduce the more severe adverse effects of lead on the hematologic system of subjects with the *ALAD 1-1* genotype, by improving their iron nutritional status.

Many investigators have reported that most Asians have the *ALAD 1-1* genotype (Lee et al. 2001; Onalaja and Claudio 2000; Ziemsen et al. 1986). The Korean subjects comprising the population of the present study confirmed that tendency. The combined risks of marginal iron nutritional status found previously by Kim et al. (2003) and the higher prevalence of *ALAD 1-1* isotype among Koreans together result in Korean lead workers being at greater risk of lead toxicity in the hematologic pathway. Therefore, careful nutritional intervention as a secondary prevention strategy for reducing the risk of lead toxicity needs to be developed while considering the *ALAD* genotypes involved.

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