IJOEM
International Journal of Occupational and Environmental Medicine

Brief Report

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Effects of delta-Aminolevulinic Acid Dehydratase Gene Polymorphism on Hematological Parameters and Kidney Function of Lead-exposed Workers

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Abstract

Lead exposure is associated with several health hazards among workers with different individual responses. We conducted this study to determine the possible effects of lead exposure on hematological parameters and kidney function of a group of Egyptian ammunition workers and the interaction of aminolevulinic acid dehydratase (ALAD) G177C gene polymorphisms as an effect modifier. Significant differences were observed between exposed workers with ALAD1-1 and ALAD1-2 genotypes in terms of blood lead level, hematological parameters and kidney function. It seems that δ-ALAD gene polymorphism may be an effect modifier and a marker of genetic susceptibility to lead toxicity.

Keywords: Explosive agents; Lead; Porphobilinogen synthase; Polymorphism, genetic; beta 2-Microglobulin

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Introduction

Lead is one of toxic elements found in several industries. It has long been used for ammunition because of its mass and malleability. Chronic exposure to lead has reported a variety of health effects mainly hematotoxicity through inhibition of heme synthesis enzymes such as δ-aminolevulinic acid dehydratase (δ-ALAD). Wan, *et al*, demonstrated that the measurement of δ-aminolevulinic acid (δ-ALA) is useful for biological monitoring of lead-exposed workers.[1]

Lead is also known to have certain renal toxicity. Several studies have shown that urinary retinol binding protein, urinary α_1-microglobulin and urinary β_2-microglobulin are good indicators of early renal effects of lead exposure.[2] However, exposure markers such as blood and urine lead levels or even bone lead levels could not always explain workers' health status because individual susceptibilities to lead may play an important role in its toxicology.[3]

δ-ALAD gene polymorphism is an important factor modifying human suscep-

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Received: Sep 9, 2018
Accepted: Mar 16, 2019

Cite this article as: Sobhi Siha M, Abdel-Hamid Shaker D, Saad Teleb H, Ahmed Rashed L. Effects of delta-aminolevulinic acid dehydratase gene polymorphism on hematological parameters and kidney function of lead-exposed workers. *Int J Occup Environ Med* 2019;**10**:89-93. doi: 10.15171/ijoem.2019.1629

tibility to lead toxicity through modifying the kinetics and distribution of lead in the blood, bone and internal organs. ALAD G177C gene polymorphism results in two alleles (ALAD1 and ALAD2) and three phenotypes (ALAD1-1, ALAD1-2 and ALAD2-2).[3]

Several studies have suggested that carriers of ALAD2 allele, which is less common than the ALAD1 allele, would have higher blood lead concentrations than non-carriers.[4] Other researchers, however, suggested that the impact of ALAD G177C gene polymorphism on lead only occurs in those with higher exposure levels.[1]

There are few studies on this issue in Egypt and in ammunition industry workers. We therefore conducted this study to determine the possible effects of lead exposure on some hematological parameters and kidney function among a group of Egyptian ammunition workers and the interaction of ALAD G177C gene polymorphisms as an effect modifier.

Materials and Methods

This cross-sectional study was carried out in May 2015 on 50 male workers at an ammunition factory for the production of the capsules of bullets and shells in Cairo, Egypt. The only inclusion criteria included was being employed in the unit for at least the two preceding years. Participants with renal or hematological diseases at the time of study were excluded. All workers gave informed written consent to participate in the study.

Clinical examination was performed with special emphasis on anemia and renal signs. From each participant 10 mL of venous blood was taken for investigations of red cell indices, lead level, δ-ALAD G177C gene study, and assessment of serum urea and creatinine levels. Urine samples were collected for determination of U-δ-ALA and U-β_2-microglobulin (ELISA kit).

A 916-base-pair sequence containing the ALAD1/2 polymorphic site was amplified and then cleaved with soy protein intolerance. Primer sequences were based on a previous study (forward: 5'-AGACAGACATTAGCTCAGTA-3' and backward: 5'-GGCAAAGACCACGTCCATTC-3'). PCR was done using 500 ng of genomic DNA, 0.5 µmol/L of each primer, 10× PCR buffer, 200 µmol/L of each deoxynucleotide triphosphate, 2.0 mmol/L $MgCl_2$ and 1.5 units of Taq in a 25-µL reaction volume.[5]

The study was approved by Ethical Committee of Occupational and Environmental Medicine Department, Cairo University, Egypt. No sensitive information was collected and participation was voluntary. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Statistical Analysis

SPSS® for Windows® ver 23 (IBM Corp, Armonk, NY) was used for data analysis. A p value <0.05 was considered statistically significant.

TAKE-HOME MESSAGE

- Lead exposure is associated with several health hazards among workers. Their response, however, varies from person to person.
- δ-aminolevulinic acid dehydratase (δ-ALAD) gene polymorphism may be an effect modifier and a marker for genetic susceptibility to lead toxicity.
- ALAD G177C gene polymorphism could modify the kinetics of lead in the blood and could provide a biomarker of nephrotoxicity and hematotoxicity.
- Carriers of ALAD1-1 genotype had higher blood lead level, abnormal hematological and renal function indices than carriers of ALAD1-2 genotype.

Table 1: Mean (SD) of some measured parameters in a group of lead-exposed workers based on their ALAD genotypes in lead exposed workers as regards laboratory findings.

Parameter	ALAD1-1 (n=38)	ALAD1-2 (n=12)	p value
Urinary β_2-microglobulin (µg/dL)	1.05 (0.39)	0.58 (0.25)	<0.001
Urinary δ-ALA (mg/L)	9.41 (1.90)	7.23 (1.18)	<0.001
RBC (10^6/µL)	2.60 (0.65)	3.59 (1.04)	0.005
Hb (g/dL)	10.76 (1.81)	13.13 (1.33)	<0.001
MCV (fL)	75.32 (8.68)	90.06 (7.42)	<0.001
MCH (pg)	25.34 (3.08)	30.67 (2.51)	<0.001
MCHC (g/dL)	30.26 (2.81)	33.63 (1.89)	0.001
Serum urea (mg/dL)	82.48 (18.21)	54.56 (10.77)	<0.001
Serum creatinine (mg/dL)	3.73 (1.17)	1.75 (0.64)	<0.001
Blood lead (µg/dL)	33.09 (4.29)	27.18 (3.97)	<0.001

Results

The participants had a mean age of 48.7 years. Thirty-eight (76%) workers were ALAD1-1 homozygotes; 12 (24%) were ALAD1-2 heterozygotes; and no one was ALAD2-2 homozygote, translating into an allel frequency of 88% for ALAD1 and 12% for ALAD2. Those workers with ALAD1-1 had a worse kidney function and hematological profile compared with those carrying ALAD1-2 genotype (Table 1). There were significant correlations between blood lead level and each of renal and hematological indices in two studied genotypes (Fig 1).

Discussion

The frequencies of ALAD1 and ALAD2 alleles were 88% and 12%, respectively, in accordance with a Chinese report indicating that the allele frequencies among 461 lead-exposed battery storage workers were 96% and 3%, respectively.[6]

The prevalence of the ALAD2 allele ranges from 0% to 20%, depending on the population;[1,5] Caucasians have the highest frequency of the ALAD2 allele, with approximately 18% being heterozygous for ALAD1-2, and only 1% being homozygous for ALAD2-2. In comparison, Africans and Asians have the lowest frequencies of ALAD2 allele, with few or no ALAD2 homozygotes. Egyptian population is known to be a mixture of Caucasians and sub-Saharan Africans.

The significant effect of ALAD1-1 genotype on blood lead level and renal and hematological parameters in lead-exposed workers compared with those workers with ALAD1-2 genotype, was also reported by Wan, *et al.*[1] The ALAD2 protein is more negatively charged than ALAD1 and has a higher affinity to bind the positively charged lead ion, modifying its kinetics in blood and thus protects the body against lead-induced hematopoietic and renal toxicity. Therefore, those carrying ALAD2 allele could tolerate longer and higher exposures to lead than those carrying ALAD1.[1,5]

Contrary to these findings, some early studies reported that the lead-exposed workers with ALAD1-2 genotype had higher blood lead levels than those work-

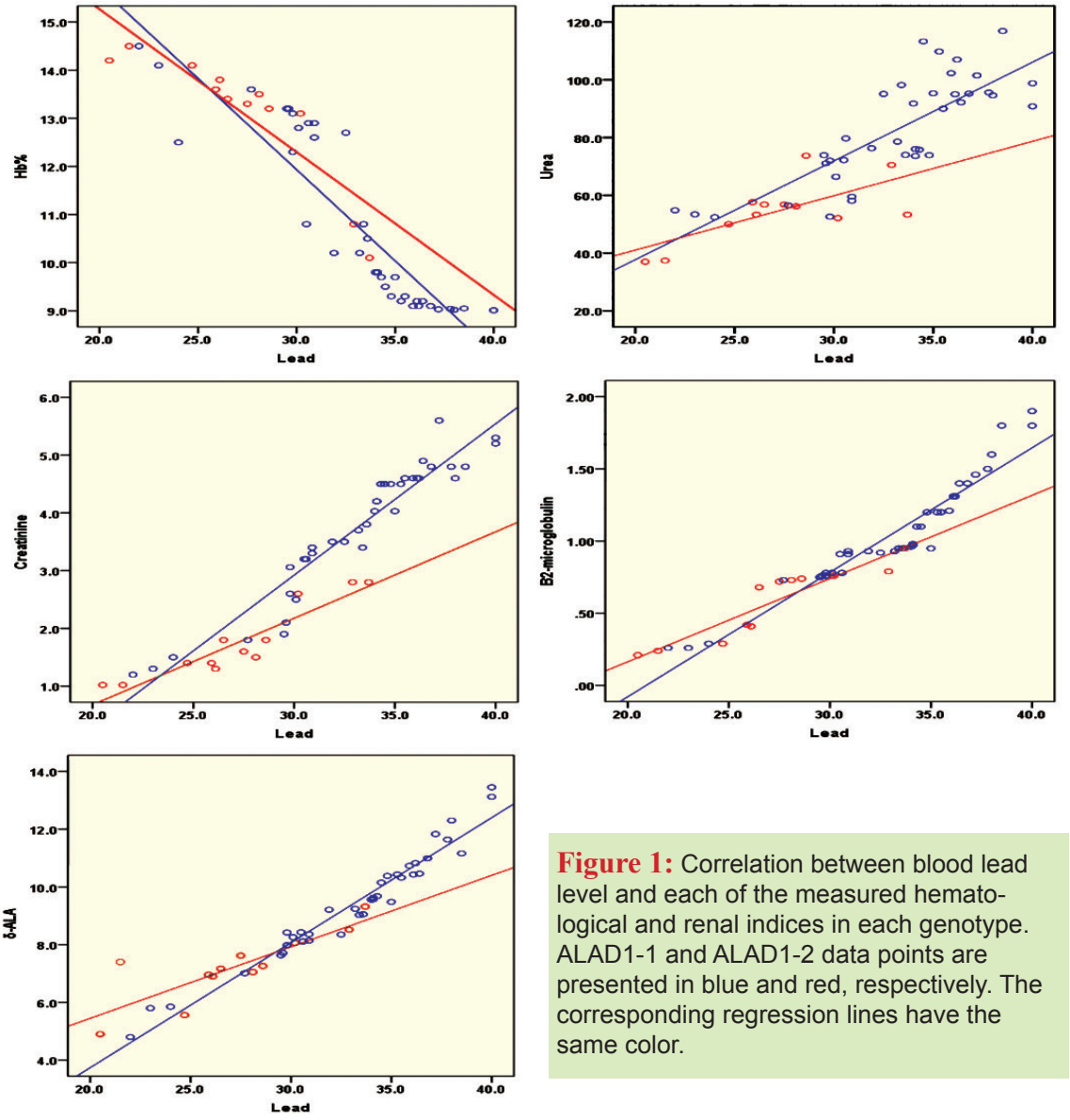

Figure 1: Correlation between blood lead level and each of the measured hematological and renal indices in each genotype. ALAD1-1 and ALAD1-2 data points are presented in blue and red, respectively. The corresponding regression lines have the same color.

ers with ALAD1-1 genotype; it was also shown that ALAD2-2 homozygotes had the highest blood lead levels.[7] However, a more recent study reported that ALAD2 carriers have a lower risk of lead toxicity than ALAD1 homozygotes at the same exposure level explained by a higher differential binding of lead to ALAD2 protein in blood cells leading to decreased sufficient amount to inhibit ferrochelatase.[8]

There were significant correlations between the blood lead level, and each of hematological and renal indices studied among both ALAD1-1 and ALAD1-2 genotypes of the exposed workers. However, the correlation was not significant for serum urea among those with ALAD1-2 gene. These results were in accordance with Weaver, *et al*,[9] who reported a positive correlations between blood lead level and renal functions among those carrying ALAD1-1 genotype. However, in contrary to what we found, they showed a negative correlation among those with ALAD1-2

gene.

Chia, *et al*, found a positive correlation between blood lead level and urinary β_2-microglobulin. They reported that the renal function of carriers of ALAD2 allele is more susceptible to the effects of lead (especially at higher levels).[4]

In conclusion, the present research proved that the ALAD G177C gene polymorphism may modify the kinetics of lead in the blood and could provide a biomarker of nephrotoxicity and hematotoxicity.

Acknowledgments

The authors would like to thank all participants in that work.

Conflicts of Interest: None declared.

Financial Support: None.

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