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Serum Neuron-Specific Enolase, Biogenic Amino-Acids and Neurobehavioral Function in Lead-Exposed Workers from Lead-Acid Battery Manufacturing Process

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Abstract

Background: The interaction between serum neuron-specific enolase (NSE), biogenic amino-acids and neurobehavioral function with blood lead levels in workers exposed to lead form lead-acid battery manufacturing process was not studied.

Objective: To evaluate serum NSE and biogenic amino-acids (dopamine and serotonin) levels, and neurobehavioral performance among workers exposed to lead from lead-acid storage battery plant, and its relation with blood lead levels (BLLs).

Methods: In a cross-sectional study, we performed biochemical and neurobehavioral function tests on 146 workers exposed to lead from lead-acid battery manufacturing process. BLLs were assessed by an atomic absorption spectrophotometer. Serum NSE, dopamine and serotonin were measured by ELISA. Neurobehavioral functions were assessed by CDC-recommended tests—simple reaction time (SRT), symbol digit substitution test (SDST), and serial digit learning test (SDLT).

Results: There was a significant correlation (r 0.199, $p<0.05$) between SDST and BLL. SDLT and SRT had also a significant positive correlation (r 0.238, $p<0.01$). NSE had a negative correlation (r −0.194, $p<0.05$) with serotonin level. Multiple linear regression analysis revealed that both SRT and SDST had positive significant associations with BLL. SRT also had a positive significant association with age.

Conclusion: Serum NSE cannot be used as a marker for BLL. The only domain of neurobehavioral function tests that is affected by increased BLL in workers of lead-acid battery manufacturing process is that of the "attention and perception" (SDST).

Keywords: Lead; Enolase, Neuron-Specific; Dopamine; Serotonin; Neurobehavioral manifestations; Biogenic amines; Amino acids; Healthy worker effect

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Introduction

Manufacturing lead-acid storage batteries involve processes, such as preparation of lead oxide, grid casting, pasting, plate cutting, formation, charging, and assembly. The chemicals lead oxide (PbO_2), spongy lead (Pb) and sulfuric acid (H_2SO_4) used in these processes, are hazardous in nature. Human exposure to lead by inhalation and ingestion[1] has potential risk; lead accumulates in erythrocytes, soft tissue (brain, kidney, and bone marrow) and mineralized tissue (bone, and teeth). Chronic lead exposure leads to a variety of health problems.[2-5] The molecular mechanism of lead-induced neurotoxicity involves blocking the receptor of N-methyl-D-aspartate, which is involved in the maturation of brain plasticity, disturbing the blood-brain barrier, and secondary messenger of calcium ions through activation of G-protein.[6] These effects cause impaired communication between astrocytes and endothelial cells, encephalopathy, and edema.

Neuron-specific enolase (NSE) is a glycolytic enzyme, enolase (2-phospho-D-glycerate hydrolysis), exists as several dimeric isoenzymes. Three isoenzymes are found in human brain—αα, αγ, and γγ. The αγ and γγ-enolase isoenzymes are also known as NSE, as these isoenzymes were initially detected in neurons and neuroendocrine cells. Serum NSE has been used as a specific marker for neuron regeneration and re-innervation.[7] The levels of serum NSE were associated with exposure to solvents,[8] chromium,[9] 1-bromopropane,[10] 2,5-hexanedione,[11] and patients with stroke and cardiac arrest.[12,13]

Serotonin and dopamine are biogenic amines. Serotonin is produced in both the central nervous system (CNS) and peripheral nervous system (PNS). In the CNS, serotonin is found to be associated with pain modulation, mood disorders, sleep disturbances, control of mood and anger, and regulation of body temperature. Serotonin produced in the PNS is associated with gastrointestinal motility and pain modulation.

Dopamine is related to the pleasure system. It promotes feelings of enjoyment and reinforcement to motivate performance. Dopamine has also functions in the brain related to motor coordination, cognition, mood, attention, and learning.

Serotonin is an inhibitory neurotransmitter, helps to calm the brain with regulation of memory, aggression, and violent behaviors. Dopamine is an excitatory neurotransmitter, associated with aggressive behaviors, and stimulates the brain.[14] Low levels of serotonin have associated with impulsive behaviors and deregulations of dopamine systems.[15]

Animal studies reported that lead exposure altered motor behavior and the synaptosomal aminergic system,[16] decreased serotonin in brain,[17-19] increased dopamine in the basal ganglia,[20] and decreased activity of neurotransmitters that ultimately affected the locomotive and cognitive functions.[21]

Increased number of errors, high response time in the symbol digit test, impaired memory,[22] and poor scores in profile of mood states, tension-anxiety, hostility, and depression[23] have been reported in lead smelter workers. Mild neurobehavioral dysfunctions were also noticed in those exposed to lead from printing house.[24] The lead exposure affected the simple reaction time, digital symbol, correct dots and total dots.[25] There are reports in lead battery workers on autonomic nervous system disorders,[26] mood and motor coordination disturbances,[27] alterations of dopamine and its metabolite, homovanillic acid, in urine associated with impaired neurobehavioral function,[5] and poor scores for digit symbol, Bourdon-Wiersma, trail making test (part A), Santa Ana test, flicker fusion and simple reaction time,[28] slow performance in psychomotor tasks, impaired processing of visual-spatial information, reduced memory and learning functions, low performance in doing accurate tasks, slow execution of responses, and poor attention control.[29]

So far, the interactions between serum NSE, biogenic amines and neurobehavioral function tests in workers exposed to lead from lead acid-storage battery manufacturing processes have not been studied. We therefore, conducted this study to evaluate the serum NSE and biogenic amino-acids (dopamine and serotonin) levels, and neurobehavioral function among workers exposed to lead from lead acid-storage battery manufacturing process.

Materials and Methods

In a cross-sectional study, we examined 146 workers exposed to lead from lead-acid battery manufacturing plant from Tamil Nadu, India. The serum NSE and biogenic amino-acids levels, and neurobehavioral function tests among lead-exposed workers were determined and compared in two categories of workers stratified by their blood lead levels (BLLs) using the cut-off value of 25 µg/dL set by CDC-NIOSH (ABLES),[30] Adult Blood Lead Epidemiology and Surveillance.

TAKE-HOME MESSAGE

- Human exposure to lead by inhalation and ingestion caused accumulation of lead in erythrocytes, soft tissue (brain, kidney, and bone marrow) and mineralized tissue (bone, and teeth).
- The most common neurological complaint of lead-exposed workers was irritability.
- Serum NSE level increased with decrease in serotonin level. It cannot be used as a marker for BLL.

Before including the workers in the study, an informed written consent was obtained from each of them. Personal habits of studied workers such as alcohol consumption, smoking, dietary pattern, occupational history, and subjective neurological complaints were recorded in a pre-designed questionnaire.

Three mL of venous blood was collected in heparinized vacuette from studied workers and stored at −20 °C until analysis. Two mL of the blood sample was digested by a microwave digestion system (ETHOS-D, Italy) with 2 mL of nitric acid (HNO_3) and 0.2 mL of hydrogen peroxide (H_2O_2). The digested samples were made up to 5 mL using triple distilled water and centrifuged. The BLL was measured by an atomic absorption spectrophotometer (GBC-Avanta, Australia). Twenty µg/dL of the standard solution was prepared from the lead standard solution (Merck 1.19776.0500) and added to the lowest concentration of the sample. The analysis found 100% recovery with %RSD at <0.5 for three replicates.

Two mL of whole blood was collected in plain tubes and centrifuged at 3000 rpm for 10 min at 4 °C. The serum was separated and used for determination of NSE, dopamine, and serotonin.

The concentration of serum NSE was measured by ELISA (Cusabio Biotech Company Limited). The absorbance of standards and samples were measured by a molecular device microplate reader (USA) at 450 nm. The concentration of samples was determined by four parameter logistic (4-PL) regression model. The detection range was 1.56–100 ng/mL; the sensitivity was 0.39 ng/mL.

The serum dopamine and serotonin levels in lead-exposed workers were measured by ELISA (Causation Biotech Company Ltd). The absorbance of standards and samples were measured by a Molecular Device microplate reader at 450 nm.

Concentrations of samples were determined by four parameter logistic (4-PL) regression model. The detection range of dopamine was 0.5–100 ng/mL and the sensitivity was 0.25 ng/mL. The parameters for serotonin were 4–800 ng/mL, and 2 ng/mL, respectively.

Neuropsychological functions were assessed in lead-exposed workers using CDC recommended tests[31] including simple reaction time (SRT), symbol digit substitution (SDST) and serial digit learning (SDLT) tests.

Simple Reaction Time Test (SRT)

This test measures the visual motor speed and involves pressing a button when the color of an area on a screen turns from red into green. Web-based development SRT test was used (University of Washington faculty Web server). Five trials were administrated for each worker. The mean reaction time was chosen and expressed in ms. Shorter reaction time indicates better neurobehavioral performance.

Symbol Digit Substitution Test (SDST)

The test measures attention and perception. In this test, one to nine digits are paired with nine symbols in a grid. The subject matches the correct digits with jumbled symbols on a second grid. The total time taken for each person was measured and reported as the test result.

Serial Digit Learning Test (SDLT)

This test is a measure of learning recall and short memory. A string of eight numbers is presented. The subject must read, remember and enter the eight digits. A total score was calculated. If a subject's response had fewer than six of the eight digits in correct positions, two points were added to the score. One point was added when either six or seven digits were in correct positions, no extra-point was added when all eight digits were correct.

Table 1: Demographic details of lead-exposed workers. Numbers are either mean (SD) or frequency (%).

Parameters	Workers (n=146)
Age (yrs)	36.0 (4.8)
Service length (yrs)	13.2 (3.6)
BMI (kg/m^2)	25.8 (2.4)
Current smokers	33 (22.6%)
Alcohol users	78 (53.4%)
BP (mm Hg)	
Systolic <140	118 (80.8%)
Systolic ≥140	28 (19.2%)
Diastolic <90	127 (87.0%)
Diastolic ≥90	19 (13.0%)

Statistical Analysis

SPSS® for Windows® ver 17.0 was used for statistical analysis of the data. *Student's t* test was used to compare mean of the measured variables between two groups. Pearson's correlation coefficient was used to assess the relationship between BLL and serum NSE and biogenic amino-acids levels and neurobehavioral function tests results. Multiple linear regression analysis was used to evaluate the association between neurobehavioral function tests results and other studied variables. In the model, SRT, SDST, and SDLT were used as dependent variables and age, alcohol consumption, BLLs, BMI, service length, smoking, and NSE, dopamine and serotonin levels were used as independent variables. A p value <0.05 was considered statistically significant.

Results

The demographic details of workers exposed to lead are presented in Table 1. The most common neurological complaint of lead-exposed workers was irritability (Fig 1). SDST was the only neurobehavioral

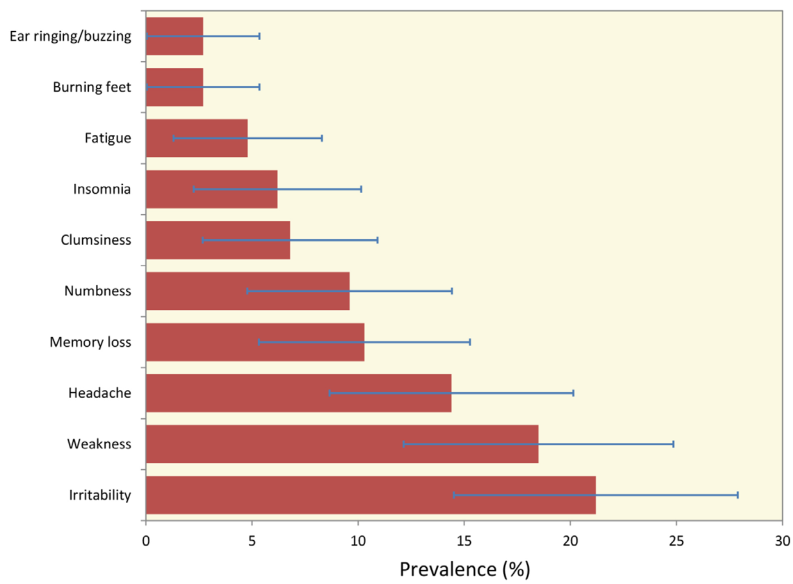

Figure 1: The prevalence of neurological complaints reported by lead-exposed workers (n=146). Error bars represent 95% CI.

function test that was significantly longer in workers with BLL >25 µg/dL compared to those with lower BLLs (Table 2). SRT, SDLT, NSE, dopamine and serotonin levels were not significantly different between the two groups.

There was a significant correlation (r 0.199, $p<0.05$) between SDST and BLL.

Table 2: Neurobehavioral function tests and neurochemical parameters in two subgroups of workers stratified by blood lead levels. Values are mean (SD).

Parameters	Blood lead levels ≤25 (µg/dL) (n=33)	Blood lead levels >25 (µg/dL) (n=113)	p value
BLL (µg/dL)	19.6 (3.4)	36.9 (6.4)	0.001
SRT (ms)	312 (43.7)	330 (54.2)	0.056
SDST (s)	36.0 (13.8)	43 (19.1)	0.025
SDLT (error score)	0.3 (0.5)	0.3 (0.5)	0.671
NSE (ng/mL)	2.5 (1.3)	3.0 (1.9)	0.187
Dopamine (ng/mL)	11.0 (6.3)	13.0 (7.4)	0.403
Serotonin (ng/mL)	107.0 (48.3)	102.0 (48.9)	0.639

SDST was also correlated (r 0.191, $p<0.05$) with dopamine level. SDLT and SRT had also a significant positive correlation (r 0.238, $p<0.01$). Dopamine and serotonin levels were also positively correlated (r 0.225, $p<0.05$). NSE had a negative correlation (r −0.194, $p<0.05$) with serotonin level.

The results of multiple linear regression analysis of variables that would affect neurobehavioral functions among lead-exposed workers are shown in Table 3. Both SRT and SDST had positive significant associations with BLL. SRT also had a positive significant association with age.

Discussion

The present study assessed the neurobehavioral function tests and serum levels of NSE, dopamine and serotonin in lead-exposed workers from a lead-acid storage battery plant. Hanninen, *et al*,[32] reported that BLLs give a more accurate prediction for the neuropsychological effects of lead.

We found that SDST was significantly associated with BLL. This finding was similar to that reported by other studies[24,33] that reported positive associations between BLL and neurobehavioral function tests in lead-exposed persons. Carta, *et al*,[22] also showed that a BLL >30 µg/dL is associated with increased number of errors and response time in SDT among lead smelter workers. Chen, *et al*,[29] showed significant impairment in neurobehavioral functions in workers with BLLs between 40 and 80 µg/dL that included slow performance of psychomotor tasks, impaired processing of visual-spatial information, reduced memory and learning functions, and resulted in slow execution of responses, and poor attention control. Balbus, *et al*[34] reported a positive association between SRT and organolead exposure.

In the current study, we found that SRT was significantly associated with BLL and

Table 3: Multiple linear regression analysis results. Values are β (p value).

Independent Variables	Dependent Variable		
	SRT (ms)	SDST (s)	SDLT (error score)
Age (yrs)	0.217 (0.029)*	0.086 (0.388)	0.059 (0.567)
Alcohol consumption	0.105 (0.227)	–0.014 (0.869)	0.003 (0.977)
BLL (µg/dL)	0.235 (0.007)**	0.199 (0.022)*	0.063 (0.480)
BMI (kg/m^2)	0.013 (0.879)	–0.090 (0.307)	0.022 (0.812)
Service length (yrs)	0.072 (0.460)	–0.002 (0.984)	0.006 (0.955)
Smoking	–0.095 (0.283)	0.158 (0.074)	–0.084 (0.361)
NSE (ng/mL)	–0.080 (0.340)	0.007 (0.938)	–0.151 (0.086)
Dopamine (ng/mL)	–0.149 (0.086)	–0.150 (0.086)	0.071 (0.432)
Serotonin (ng/mL)	–0.021 (0.808)	–0.083 (0.342)	–0.111 (0.221)
r^2	**0.128**	**0.119**	**0.045**

*p<0.05; **p<0.01

age of studied workers. Chanda Bash, *et al*,[16] also reported that lead exposure induced age-dependent alterations in motor behavior and synaptosomal aminergic system.

Originated from the brain, NSE is a protein commonly used to assess the presence and severity of neurological injury.[35] Higher levels of serum NSE reported in patients with silicosis,[36] mercury intoxication,[37] pneumoconiosis,[38] and those exposed to chromium[9] and carbon-monoxide[39]. Lower levels of serum NSE were reported in workers exposed to organic solvents,[8] and patients with major depressive and bipolar affective disorders.[40] We found that in lead-exposed workers, serum NSE level was negatively correlated with serotonin level.

Deficiencies of monoamine degradation lead to cognitive, behavioral and autonomic disorders.[41] Mansouri, *et al*,[17] reported that extracellular dopamine concentration was unaffected and serotonin concentration decreased in rats exposed to lead. Lead exposure caused a significant decrease in dopamine,[18] the levels of norepinephrine, dopamine, and serotonin in different brain regions were also altered after lead exposure.[19]

Serotonin and dopamine play opposite roles in the CNS. It has been postulated that the decrease in serotonin observed among lead-exposed persons might be due to the inhibition of the activity-associated Ca^{2+}-dependent release of neurotransmitters[14] and the disruption of serotonin storage pools, leading to the increased degradation of serotonin inside the neurons by monoamines.[42] Tang, *et al*, showed positive association between urinary homovanillic acid and BLLs, that dopamine was negatively correlated with Benton visual retention, and that homovanillic acid was negatively correlated with digit symbol, BVR, and pursuit aiming (PA) in lead-exposed workers.[5] In the present study, multiple regression analysis showed that BLLs were positively associated with SRT and SDST.

In conclusion, serum NSE level increased with decrease in serotonin level. It cannot be used as a marker for BLL. The only domain of neurobehavioral function tests that is affected by increased BLL is that of the "attention and perception" (SDST). Therefore, SDST is the only neurobehavioral function test for the assessment of BLL in those working in lead-acid battery manufacturing process.

Conflicts of Interest: None declared.

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