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LEAD-INDUCED NEUROTOXICITY AMONG OCCUPATIONALLY-EXPOSED WORKERS: MOLECULAR EFFECTS AND CLINICAL CORRELATES

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ABSTRACT

Rationale and background: Lead [Pb(II)] affects the higher functions of the central nervous system and undermines brain growth, preventing the correct development of cognitive and behavioral functions at exceedingly low levels of exposure.

Aim of the work: The aim of the present study was to evaluate the possible lead-induced neurological affections and their mechanism of occurrence.

Subjects and methods: For this purpose, 42 subjects were included in this study and classified into 2 groups: Group I: Included 20 employees working in the wet battery factory (not exposed to lead) and Group II: 22 workers in the same factory working in the wet battery paste. After history taking and full clinical examination about the possible lead-induced toxic effects, ten milliliters of venous blood were collected from every subject, centrifuged and the serum was used for the estimation of blood lead level, serum tumor necrosis factor α (TNF α), serum interleukin1 (IL1), metalloproteinase-9.

Results: Cases had statistically significant higher TNF α, IL1 and metalloproteinase-9 than controls.

Conclusion and recommendation: Lead could produce its neurotoxic effects, presented in the current work by the statistically elevated TNF α, IL1 and metalloproteinase-9, through altering the normal immune pattern of the nervous system. This study had provided important new insights into the molecular mechanisms of metal toxicity and had opened several exciting avenues of research.

Introduction

Lead is the most widely used metal, the use of lead compounds still play an important role in modern industry. There has been a marked increase in its use since the 1950s. Despite widely applied restrictions on major uses of lead (e.g.., gasoline additives, paints, and cans); the current annual worldwide production is approximately 5.4 million tons, 23% of which is produced in the United States. Sixty percent of lead is used for the manufacturing of batteries (automobile batteries, in particular), while the remainder is required for the production of pigments, solder, plastics, cable sheathing, ammunition, and a variety of other extruded products (Fischbein, 1998).

Lead is a hazardous metal for all humans. Lead toxicity causes hematological, gastrointestinal, and neurological dysfunction. Symptoms are usually noted when blood lead greater than 2 micromoles/L. Severe or prolonged exposure may also cause chronic nephropathy, hypertension, and reproductive impairment. Lead inhibits some enzymes, alters cellular calcium metabolism, stimulates synthesis of binding proteins in kidney, brain, and bone, and slows down nerve conduction (Patocka & Cerny, 2003).

It has become increasingly evident that the field of neurotoxicology is not only rapidly growing but also rapidly evolving, especially over the last 20 years. As the number of drugs, environmental, bacterial/viral agents with potential neurotoxic properties has grown, the need for additional testing has increased. Only recently has the technology advanced to a level that neurotoxicologic studies can be performed without operating in a "black box." Examination of the effects of agents that are suspected of being toxic can occur on the molecular (protein-protein), cellular (biomarkers, neuronal function), and genetic (polymorphisms) level. Together, these areas help to elucidate the potential toxic

profiles of unknown (and in some cases, known) agents. The area of proteomics is one of the fastest growing areas in science and particularly applicable to neurotoxicology (Marchetti, 2003).

Cellular neurotoxicology involves many cellular processes including alterations in cellular energy homeostasis, ion homeostasis, intracellular signaling function, and neurotransmitter release, uptake, and storage. The greatest hurdle in cellular neurotoxicology has been the discovery of appropriate biomarkers that are reliable, reproducible, and easy to obtain. There are biomarkers of exposure effect, and susceptibility. Finding the appropriate biomarker for a particular toxin is a daunting task. The advantage to biomarker/toxin combinations is they can be detected and measured shortly following exposure and before overt neuroanatomic damage or lesions. Intervention at this point, shortly following exposure, may prevent or at least attenuate further damage to the individual. The use of peripheral biomarkers to assess toxin damage in the CNS has numerous advantages: time-course analysis may be performed, ethical concerns with the use of human subjects can partially be avoided, procedures to acquire samples are less invasive, and in general, peripheral studies are easier to perform (Wallace, 2005).

Exposure of cells to inorganic lead (Pb) at concentrations above the currently accepted biological limitations has been shown to be associated with a variety of neurological disturbances (Cory-Slechta, 1995). In addition to the lead-induced peripheral neuropathy, central nervous system (CNS) pathologies including inflammation, blood-brain barrier (BBB) failure leading to brain edema, damage of neurons and ultimately gliosis have been reported (Rosenberg, 1995). It has been suggested that interaction between lead and proteins, which interrupt intracellular calcium pathways, is the basis of the lead-mediated CNS cytotoxicity. Lead accumulates primarily in astrocytes; however, the glial cells appear to be less sensitive to its cytotoxic effects than other CNS cell types such as neurons. The morphological, transcriptional and translational changes observed in astrocytes containing Pb were suggested to be direct result of damage induced by Pb or, alternatively, they may represent cellular adaptive responses to Pb accumulation (Lahat et al., 2002).

Tumor necrosis factor α (TNF α) regulates a variety of biologic functions, including organ development, immune ho-

meostasis, and malignancy. The body subtly regulates the expression kinetics and dose of TNF α to ensure its proper effect because TNF α has opposite biologic effects in different circumstances (Aggarwal, 2003 and Pfeffer, 2003). On the one hand, TNF α is essential for the host in tissue repair and in protective immune responses against infection. On the other hand, inadequate TNF α may have detrimental consequences in sepsis, tumor formation, and autoimmune diseases. Regulating the expression of TNF α has been an important subject in managing acute inflammatory diseases that include bacterial sepsis (Cheng et al., 2006).

The matrix metalloproteinases (MMPs), an important family of proteases associated with basement membrane (BM) and extracellular matrix (ECM) remodeling, are involved in both physiological and pathological CNS processes (Lahat et al., 2002).

Members of this family, the gelatinases (MMP-2 and MMP-9) are particularly implicated in CNS deleterious effects, such as blood brain barrier (BBB) eruption enabling transmigration of immune cells associated with edema, myelin degradation, and glioblastoma dissemination. MMP-9 produced by CNS and infiltrating-immune cells is enhanced by pro-inflammatory cytokines and elevated levels of this MMP-9 have been correlated with disease activity (Miller et al., 2002).

The aim of the present study was to evaluate the possible lead-induced neurological affections and their mechanism of occurrence.

Subjects and Methods

This study was carried out on workers in a wet battery factory. Workers exposed to other chemical compounds than Lead, those taking drugs affecting the CNS or immunosuppressing drugs were excluded. All workers gave their informed consent to participate in the study.

Thorough history taking was obtained from each worker with special inquiry about symptoms pointing to lead toxicity e.g. neurological manifestations (numbness, tingling, muscle weakness and impotence), psychiatric manifestations (headache, depression). Also, careful clinical examination was done with stress on CNS examination, including sensory, motor and cranial nerve affection.

They were classified into 2 groups:

Group I: The control group was formed of 20 male employees working in

the battery factory but not exposed to any chemical.

N.B.: Wet battery paste is made by mixing the lead oxide with water and sulphuric acid.

Group II: Included 22 male workers working in the battery paste section (exposed case group).

Both groups were working 8 hours/ daily, 5 days/weekly and, they were all smokers, non-diabetic, normotensive. All cases were having blue lines in their gums.

Sampling:

Ten milliliters of venous blood were collected from every subject 5ml for detection of blood lead level, other 5ml centrifuged and the serum was stored in the deep freeze at -10˚c till its use. The following investigations were performed for every worker:

Estimation of blood lead levels:

I- Estimation of blood lead levels

II- Tumor necrosis factor α (TNF α).

III- Interleukin1 (IL1).

IV- Matrix metalloproteinase (MMP9).

Lead levels were estimated using a flameless atomic absorption spectrophotometry (Varian SpectrAA 220) equipped with a graphite furnace Auto-sampler (GTA-110). The spectral line used for Pb determination was 283.3 nm. according to the method described by Fernandez (1975).

Measurement of TNF α and IL1 was done using commercially available enzyme immuno-assay (EIA) kits according to manufacturer's instruction (cytoimmune sciences incorporation college park, MD, USA).

Briefly serum samples and kit calibrator were incubated with monoclonal antibodies for 2 hours at room temperature. The resulting immune complexes were bounded on the wall of the plate, the unbounded reactants were removed by washing steps, next the plate was incubated with the enzymatic reagent to develop the color, the absorbance of the color then detected by ELISA reader, finally the concentration of the samples were calculated from the standard curve.

Estimation of MMP-9:

The MMP-9 instant ELISA is an enzyme-linked immunosorbent assay for quantitative detection of human MMP-9 in cell culture human serum provided by Bender MedSystems (BMS2014INST).

The Statistical Analysis:

Data were statistically described in terms of range, mean, standard deviation (SD), frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using Mann Whitney U test for independent samples. For comparing categorical data, Chi square $^{(2)}$ test was performed. Yates correction was used instead when the frequency is less than 10. Correlations between various variables were done using Spearman correlation (R). P-values less than 0.05 were considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program.

Results

Descriptive data:

The age in group I & II ranged between 23-52 years and 23-56 years with means of 37 ± 10 and 38 ± 12.1 years respectively (Table-1).

The duration of exposure in group II ranged between 3-36 years with a mean of 16.7 ± 11.8 years (Table-1).

The blood lead level in group I & II ranged between 6.2-15 μg/dl and 77-90.1 μg/dl with means of 11.9 ± 2.9 μg/dl and 83 ± 3.8 μg/dl respectively (Table-1) (Figure-1).

The serum MMP level in group I & II ranged between 22-80 ng/ml and 115-250 ng/ml with means of 55.4 ± 15.8 ng/ml and 197.9 ± 55.4 ng/ml respectively (Table-1) (Figure-2).

The serum TNF α1 level in group I & II ranged between 31.2-72.6 pg/dl and 79.8-126.4 pg/dl with means of 50.3 ± 17.2 pg/dl and 104 ± 14.7 pg/dl respectively (Table-1) (Figure-3).

The serum IL1 level in group I & II ranged between 87.3-117.3 ng/dl and 102-521.3 ng/dl with means of 102.7 ± 8.2 ng/dl and 356.3 ± 133.7 ng/dl respectively (Table-1) (Figure-4).

There was a statistically significant higher recurrent infections (in the form of recurrent styes and recurrent urinary tract infections) in cases than in controls ($p<0.0001$*) (Table-2).

There was a statistically significant higher motor nerve affection (in the form of motor weakness, wrist and foot drop) in cases than in controls ($p<0.0001$*) (Table-2).

There was a statistically significant higher cranial nerve affection (in the form of diplopia) in cases than in controls ($p<0.037^*$) (Table-2).

There was a statistically significant higher impotence level in cases than in controls ($p<0.037^*$) (Table-2).

There was a statistically significant higher blood lead level in cases than in controls ($p<0.0001^*$) (Table-1).

There was a statistically significant higher serum MMP level in cases than in controls ($p<0.0001^*$) (Table-1).

There was a statistically significant higher serum TNF $\alpha 1$ level in cases than in controls ($p<0.0001^*$) (Table-1).

There was a statistically significant higher serum IL1 level in cases than in controls ($p<0.0001^*$) (Table-1).

Mann-Whitney Comparison Test:

There was no difference in the lead level between cases having sensory, motor, cranial nerve affection and increased intracranial tension and, those with no manifestations concerning these neurological parameters (Table-4).

Spearman's Correlation:

There was a positive correlation between the lead level and the duration of exposure, MMP, TNF $\alpha 1$, and IL1 ($p<0.01^*$, $p<0.02^*$, $p<0.0001^*$ and $p<0.0001^*$ respectively (Table-3).

Table-1: Descriptive data (Minimum, maximum and Mean S±D) of age (years) and duration of exposure (years) blood lead levels (mg/dl), MMP (ng/ml), TNF α (pg/dl) and IL1 (ng/dl) in group I and II as well as their statistical significance.

Variable	Group	Minimum	Maximum	Mean ± S.D	Statistical significance (p-value)
Age	Group I	23	52	37 ± 10	0.773
	Group II	23	56	38 ± 12.1	
Exposure (years)	Group I	-	-	-	0.0001*
	Group II	3	36	16.7 ± 11.8	
Lead	Group I	6.2	15	11.9 ± 2.9	0.0001*
	Group II	77	90.1	83 ± 3.8	
MMP	Group I	22	80	55.4 ± 15.8	0.0001*
	Group II	115	250	197.9 ± 55.4	
TNF	Group I	31.2	72.6	50.3 ± 17.2	0.0001*
	Group II	79.8	126.4	104 ± 14.7	
IL1	Group I	87.3	117.3	102.7 ± 8.2	0.0001*
	Group II	102	521.3	356.3 ± 133.7	

* = significant difference

Table-2: Chi-square test (Number and percentage) of persons having and not having recurrent infections, sensory & motor manifestations, cranial nerve involvement, manifestations of increased intracranial tension and impotence in group I and II as well as their statistical significance.

Variable	Group	Number & Percentage of persons having	Number & Percentage of persons not having	Statistical significance (p-value)
Recurrent infections	Group I	- (0%)	20 (100%)	0.0001*
	Group II	14 (63.64%)	8 (36.36%)	
Sensory affection	Group I	- (0%)	20 (100%)	0.139
	Group II	8 (36.36%)	14 (63.64%)	
Motor affection	Group I	- (0%)	20 (100%)	0.0001*
	Group II	16 (72.73%)	6 (27.27%)	
Cranial nerve affection	Group I	- (0%)	20 (100%)	0.037*
	Group II	6 (27.27%)	16 (72.73%)	
increased intracranial tension	Group I	- (0%)	20 (100%)	0.0001*
	Group II	14 (63.64%)	8 (36.36%)	
Impotence	Group I	- (0%)	20 (100%)	0.037*
	Group II	6 (27.27%)	16 (72.73%)	

* = significant difference

Table-3: Spearman's Rank order correlation between the blood lead levels (μg/dl) and, exposure duration (years), MMP (ng/ml), TNF α (pg/dl) and IL1 (ng/dl) in group II as well as their statistical significance.

Pair of Variables	Number of cases	Spearman R	P-value
Exposure duration and Lead	22	0.505696	.016350*
MMP and Lead	22	-0.467197	0.028361*
TNF α and Lead	22	0.672727	0.000603*
IL1 and Lead	22	0.727273	0.000126*

* = significant difference

Table-4: Mann-Whitney U test of persons having (group 2) and not having (group 1) sensory & motor manifestations, cranial nerve involvement and manifestations of increased intracranial tension in group II according to their blood lead levels (μg/dl) as well as their statistical significance.

Variable	Rank sum group 1	Rank sum group 2	U	Z	P-level	Adjusted Z	P-level
Sensory affection	153	100	48	-0.5460	0.58505	-0.54772	0.58388
Motor affection	69	184	48	0.00	1.0000	0.000	1.0000
Cranial nerve affection	164	89	28	-1.4744	0.1403	-1.47902	0.139
increased intracranial tension	92	161	56	0.00	1.0000	0.00	1.0000

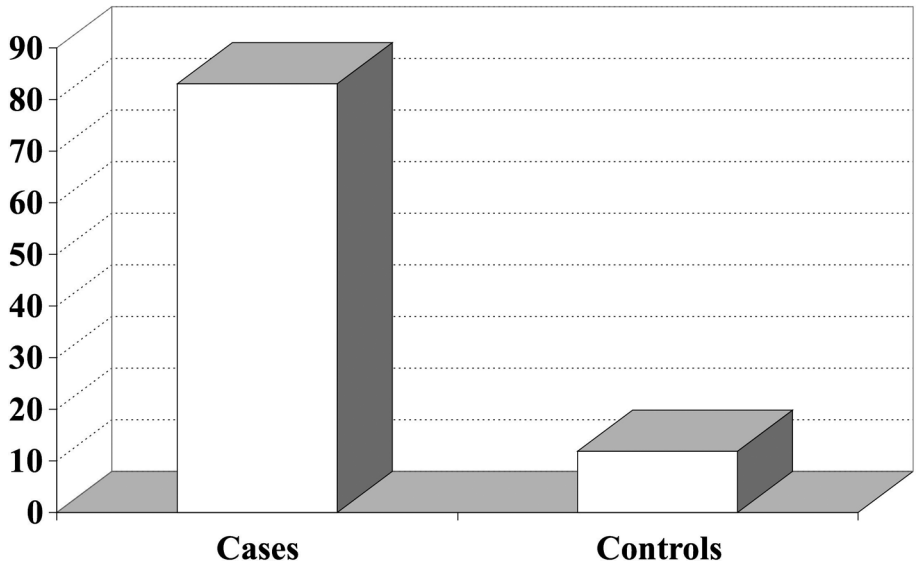

Figure (1): Mean values of blood lead (μg/dl) in cases and controls.

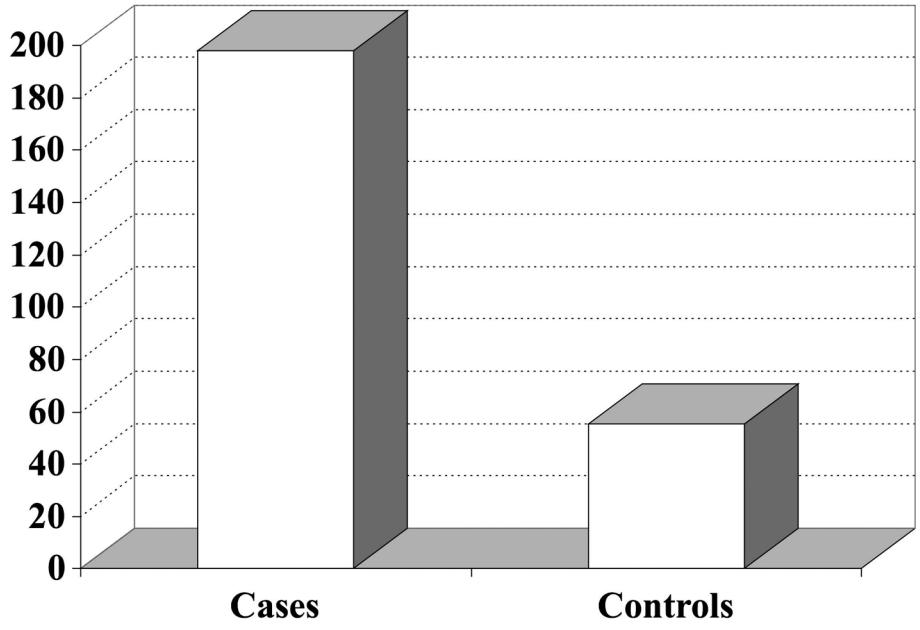

Figure (2): Mean values of serum MMP (μg/ml) in cases and controls.

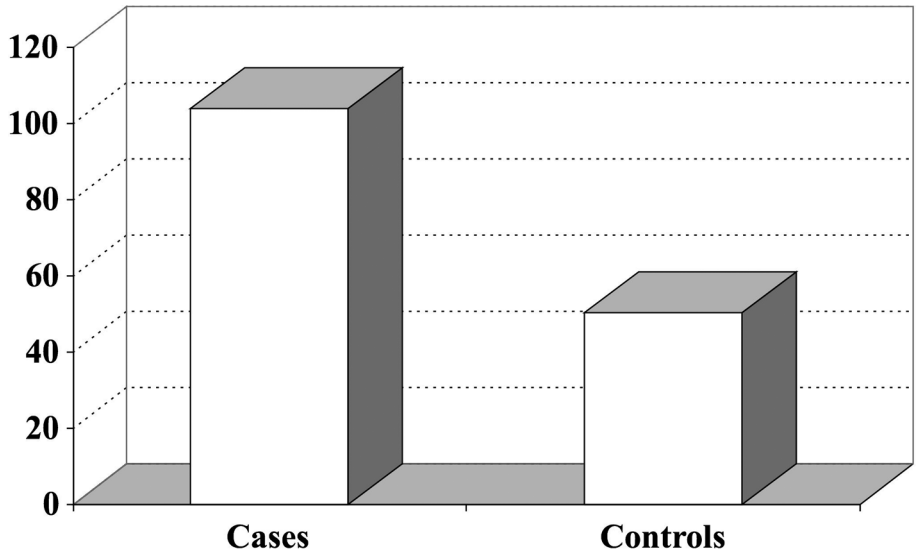

Figure (3): Mean values of serum TNF α (pg/dl) in cases and controls.

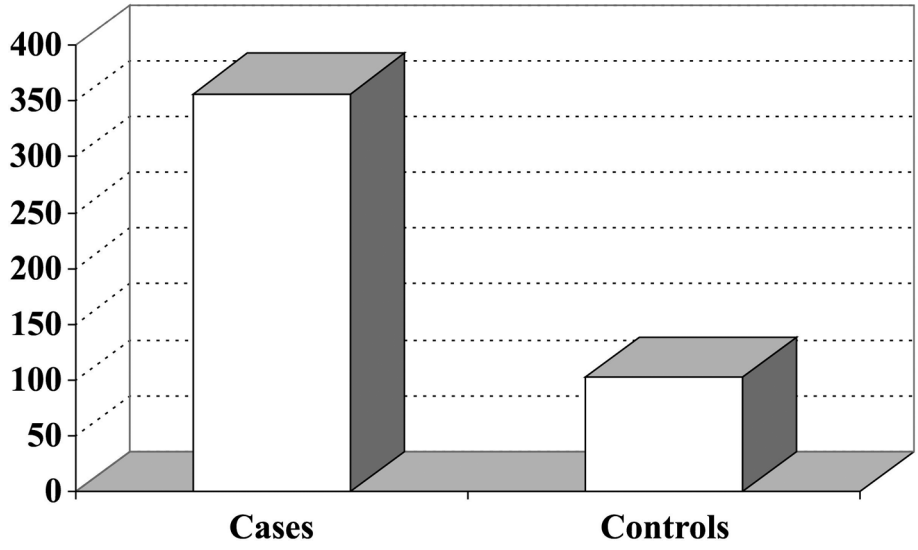

Figure (4): Mean values of serum IL1 (ng/dl) in cases and controls.

Discussion

The detrimental effects of lead poisoning have been well known since ancient times, but some of the most severe consequences of exposure to this metal have only been described recently. Lead [Pb(II)] affects the higher functions of the central nervous system and undermines brain growth, preventing the correct development of cognitive and behavioral functions at exceedingly low levels of exposure (Lidsky & Schneider, 2003).

During the last two decades, advances in behavioral, cellular and molecular neuroscience have provided the necessary experimental tools to begin deciphering the many and complex effects of Pb(2+) on neuronal processes and cell types that are essential for synaptic plasticity and learning and memory in the mammalian brain (Toscano & Guilarte, 2005).

In the present study, there were statistically significant higher lead levels in group II (cases) when compared to group I (control). Surprisingly enough all exposed cases had blue lines in their gums (lead lines).

Moreover, cases had statistically significant higher tumor necrosis factor α (TNF α) and interleukin1 (IL1) levels when compared to controls.

In our present study, cases (group II) had statistically significant higher recurrent infections, motor and cranial nerve affection and impotence than controls (group I).

Our results were in accordance to those of Zhao & Schwartz (1998). They found that the glial cells, the predominant CNS-antigen presenting cells, are involved in local inflammatory processes by responding to, as well as producing, cytokines such as interleukin (IL-1', IL-6, and tumor necrosis factor α.

On the same ground, Ferlito et al. (2001), Hsu & Wen (2002) and Cheng & Liu (2005) commented that, lead (Pb) increases lipopolysaccharide (LPS)-induced tumor necrosis factor-alpha (TNF-alpha), nitric oxide (NO), lipid peroxidation (LPO). The co-exposure of Pb and LPS significantly increased phosphorylation of TNF α alpha expression in peripheral blood cells.

In addition, Lu et al. (1997) reported that tumor necrosis factor-alpha (TNF α alpha) and interleukin-1 (IL-1) are two cytokines that are released by macrophages during the early inflammatory phase of nerve injury. Both cytokines play a role in frustrating functional nerve regeneration after injury.

Furthermore, Cheng et al. (2004) and Cheng et al. (2006) demonstrated that exposure to Pb activates protein kinase C (PKC) in several types of cells, such as astrocytes and neuronal cells in the brain. Pb stimulates PKC to activate p42/44 Mitogen activated protein kinase (MAPK), which results in the expression of TNF α in glial cells.

As an established neurotoxin, Pb(II) crosses the blood-brain barrier rapidly and concentrates in the brain. The mechanisms of lead neurotoxicity are complex and still not fully understood, but recent findings recognized that both Ca (II) dependent proteins and neurotransmitters receptors represent significant targets for Pb(II). In particular, acute and chronic exposure to lead would predominantly affect two specific protein complexes: protein kinase C and the N-methyl-D-aspartate subtype of glutamate receptor. These protein complexes are deeply involved in learning and cognitive functions and are also thought to interact significantly with each other to mediate these functions (Marchetti, 2003; Lidsky & Schneider, 2003; Vazquez & de Ortiz, 2004 and Toscano & Guilarte, 2005).

Another proposed mechanism of lead toxicity is that certain cell adhesion molecules, particularly the cadherins family of Ca(2+)-dependent cell adhesion molecules and the immunoglobulin family of Ca (2+)-independent cell adhesion molecules, may be important early targets on which Pb act to produce its toxic effects affecting learning and memory and, immune responses (Prozialeck, et al., 2002).

The health risks associated with exposure to heavy metals such as lead (Pb) remain a major public health concern. The zinc finger protein (ZFP) is a major structural motif involved in protein-nucleic acid interactions and is essential for regulation of gene expression in the developing brain. Lead exposure perturbed the DNA-binding of ZFP such as N-methyl-D-aspartate amino acid receptor (NMDAR) in the cerebellum, which plays a critical role in CNS development resulting in adverse cellular effects (Zawia et al., 2000; Razmiafshari, et al., 2001 and Basha et al., 2003).

In the current study, cases had statistically significant higher MMP-9 than controls. Our results were in agreement to those previously obtained by Lahat et al. (2002). They observed an increase in MMP-9 secretion despite the decrease in glial cell number, exposed to lead, suggesting the involvement of a non-cytotoxic mechanism in the combined Pb and pro-

inflammatory cytokines-mediated MMP-9 induction in the glial cells. They reported Pb-mediated pro-inflammatory and non-cytotoxic effects on immune cells manifested by increased T cell proliferation and cytokine secretion, enhanced production of antibodies by B cells, and elevated expression of MHC class II on antigen-presenting cells. They concluded synergistic interactions between Pb and inflammatory cytokines that alter the characteristics of CNS cells leading to the pathological cascade of BBB permeability, brain edema and cellular apoptosis.

In addition, Yong et al. (1998) concluded that both TNF α and IL-1 are potent inducer of proteinases in the CNS e.g. MMP-9.

Conclusion and Recommendations:

From this study we can conclude that Lead can produce its neurotoxic effects, presented in the current work by the statistically elevated TNF α, IL1 and metalloproteinase-9, through altering the normal immune pattern of the nervous system.

All hardly affected workers should be referred to hospital for treatment, receive chelating agent and should be away from work for a period of time till their improvement.

All exposed workers should be routinely investigated for their MMP9 level every 6 months to pick up early changes before manifest neurological affection.

These studies have provided important new insights into the molecular mechanisms of metal toxicity and have opened several exciting avenues of research.

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