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Analyzing the association between lead exposure and Alzheimer's disease in Karbala province

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ABSTRACT

Background: Alzheimer's disease (AD) is a neurodegenerative illness that is rising in the older population. The disease is related with industrially produced hazardous substances. Long-term exposure to several metallic materials is a well-established etiological risk factor that has grown more prevalent as a result of the high rate at which human activities release substantial quantities of metals into the environment. Specifically, heavy metals are extremely harmful to the nervous system. Multiple studies have linked the toxicity of heavy metals such as mercury, lead, and cadmium to neurofibrillary tangles, amyloid beta peptide aggregation, and neuronal cell death. The purpose of this study was to evaluate the differences in Serum lead levels between AD patients and healthy subjects. **Methods:** This study was conducted on all patients with cognitive impairment who were referred to AL Husain Medical City following a diagnosis by a professional psychiatric and neurological consultant in accordance with National Institute on Aging and Alzheimer's Association guidelines. Patients and controls were matched by age and gender. Serum lead levels were determined for both groups using flameless atomic absorption spectrometry (SHIMADZU AA-6300/Japan) . **Results**: The average values of serum lead levels in the patients and healthy controls were (19.13±19.11ppb) and (10.22±2.49ppb) respectively with showed differences of high statistical significance ($p< 0.001$). **Conclusion:** In this work, serum lead levels were strongly related with AD.

Keywords: Heavy metals, lead exposure, Alzheimer’s disease.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that gets worse over time. Its symptoms show up in older people and characterized by memory loss and language impairment. (1) There are about 47 million persons with dementia in the world. As the population ages, that figure is projected to climb to more than 131 million by 2050.(2) It has been calculated that between 138 599 and 182 752 persons in Iraq suffer from AD.(3) As cognitive functions slowly get worse over time, the patient loses the ability to do daily tasks and personal things on his or her own and becomes more reliant on others. This makes the patient feel less good about himself or herself and might cause stress and sadness.(4) The

primary etiology of AD remains uncertain, but it is thought that a combination of genetic factors and environmental factors may induce amyloid beta (Aβ) protein to accumulate between brain cells, which is thought to be a cause of the disease.(5) The amyloid precursor protein (APP) is the source of Aβ . One of the most notable features of Alzheimer's disease is the buildup of this protein in the brain in the form of plaque.(6)

The neuropathological hallmarks of Alzheimer's disease are the neurofibrillary tangles (NFTs) and plaques formed when two crucial brain proteins, Aβ and tau misfold and clump together. Soluble APPα, a non-pathogenic protein fragment of APP, abundance in a normal brain and is generated by alpha secretase cleavage. (7) However, APP cleavage by beta and gamma secretase results in the manufacturing of harmful Aβ component in the AD brain. Which are susceptible to mis-folding and the formation of oligomers, which are the most poisonous Aβspecies. (8)

A variety of modifiable lifestyle variables, such as dietary choices and exposure to both environmental and occupational threats, might impact an individual's chance of developing AD. (9) Historically, heavy metals have been abundant, dense, and massive atoms. However, several heavy metals, like mercury, lead, and cadmium, have no established biological role but are very harmful when ingested by animals (including humans), and are thus classified as toxic heavy metals.(10) According to the World Health Organization, lead, cadmium, and mercury are three of the ten most hazardous substances to public health. (11) and exposure to these metals has been linked to a variety of neurodegenerative and neurodevelopmental disorders in humans (12)

Lead is a toxic metal that occurs naturally in the Crust of the earth. Its wide use has caused a lot of damage to the environment, human exposure, and big problems with public health in many parts of the world.(13) Both occupational and environmental sources can expose people to lead, which can then be absorbed into the body by inhalation of lead dust created when lead-containing objects are burned, or through ingestion of dust, water, or food that has been contaminated with lead.(14) Once lead enters the body, it binds to circulating erythrocytes with a half-life of 30 days and is distributed to organs such as the brain, kidneys, and liver, eventually accumulating in bone with a half-life of 20 to30 years.(15) Serum lead levels tend to rise during breastfeeding , menopause, pregnancy, and aging as a result of an increase in bone demineralization, which results in the release of lead from storage.(16)

There is evidence to suggest that the estimated 1% of the global burden of disease attributable to lead is an underestimate, as are the long-lasting consequences on children's IQ and behavioral issues.(17) Adult neurodegenerative diseases like AD, amyotrophic lateral sclerosis, and Parkinson's are more likely to happen in older people who have been exposed to lead. These diseases cause cognitive decline and dementia.(18) Lead readily penetrates the blood brain Barrier and accumulates in the brain mostly owing to its capacity to replace calcium ions (Ca^{2+}). It does this by interfering with calcium's regulatory roles in brain cells, which disrupts its intracellular functions, causing nonspecific brain disruption and neurotoxicity (19) The overproduction of free radicals caused by lead exposure is also linked to neurotoxicity. This is because it changes the way the brain works since cellular antioxidant defenses are compromised by thiol depletion and subsequent oxidative stress. This causes endoplasmic reticulum stress, damage to the mitochondria, and the death of neurons.(19)

A lot of studies have shown that either long-term or short-term lead exposure can cause the classic signs of AD such as tau pathology, accumulation of Aβ, α-synuclein and inflammation.(20) the exposure to lead in an young period time in life resulted in increased expression of APP, β-secretase 1 and transcription factors-specific protein 1 that afterward prompted AD-like pathological changes by triggering Aβ deposition and plaque formation inside the cortex and hippocampus parts of the brain and

cause the stimulation of apoptosis thus autophagy. (21) Lead exposure is also linked to the excitation of glial cells and the increased production of pro-inflammatory protein molecules, both of which are known to be related to the neuronal damage in the brains of people with AD.(22)
To find out more about the possible role of circulating blood lead levels in the cause of AD, we looked to see if they were the same in people with AD and healthy controls.

Materials and Methods

Patients and Controls

A case-control study was conducted between December 2021 and September 2022 in the laboratories of Al-Kafeel Specialized Hospital and the advanced postgraduate laboratories of the biochemistry department in the Medicine College at Karbala University, Karbala, Iraq. This study comprised seventy people with dementia as well as sixty seemingly healthy controls match in gender and age. The samples were collected from the psychiatrist and neurologist departments in AL Husain Medical City after a diagnosis of dementia by a specialist psychiatric and neurological consultant . Exclusion criteria included a family history of dementia, the presence of another neurologic condition that might compromise cognitive performance, and refusal to volunteer for the study. The biochemistry department's Ethics Committee at College of Medicine/University of Kerbala evaluated and approved the protocol for this study. Subjects or their primary caregivers provided written consent for blood collection by signing a consent form.

Sample Collection and Preparation

Five milliliters of venous blood were obtained by vein puncture using 5mL disposable syringes from each individual (patient and healthy control). Blood was deposited in a gel tubes and left to coagulate for 20 minutes before being centrifuged at 2900xg for 10 minutes to get serum.

Determination of lead in serum

The serum lead levels were measured by using flameless atomic absorption spectrometry (SHIMADZU AA-6300/ japan). Four standard solutions (2.5, 5, 10, and 20 ppb) of the element were prepared which used for drawing calibration curve as shown in Figure (1).

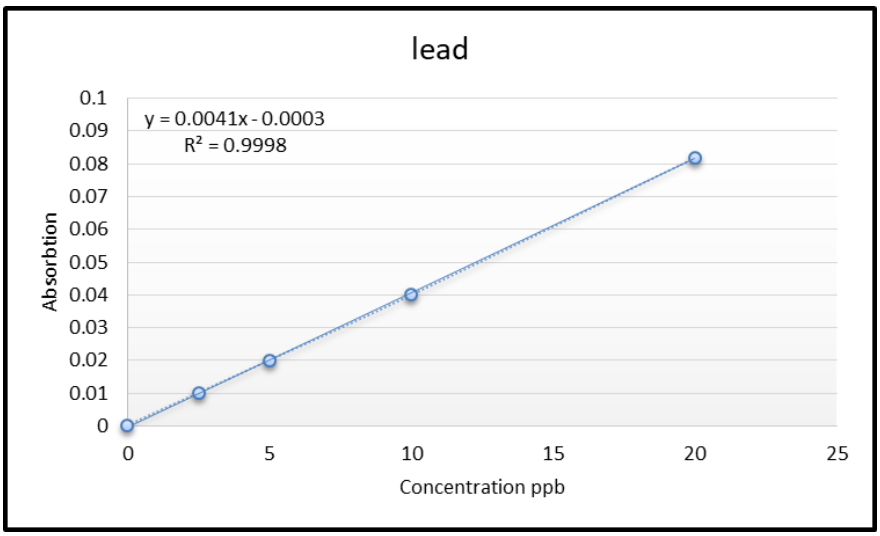


Figure (1): Standard curve for lead determination

Depending on the calibration curve, the amounts of lead in samples were assessed immediately and constantly in lieu of testing reference solutions. Table(1) has a list of the settings for lead determination.

Table (1): Ideal settings for Pb determination

Variable	Ideal condition
Atomizer	Graphite Furnace
Fuel	Argon gas
Lamp current	10 mA
Wavelength	283.3 nm
Slit width	0.7nm
Lighting mode	BGC-D2
Sample Size	20 µL

Statistical Analysis

For all statistical procedures , version 28.0 of the SPSS program was utilized (IBM: SPSS, and Chicago, Illinois, USA) On the information about the participants in each group, descriptive statistics were done. Mean 2SD was used to show the values for the continuous variable. The Shapiro test was used to check how the data were spread out. Analytical statistical tests showed that the parameters had categorical variables that were different in important ways. Statistically significant was assumed for all tests of hypothesis with a p-value of less than 0.05.

Results and Discussion

The average age of the participants ranged between (60-95) years. The gender distribution among the analyzed groups was as follows: 30 males and 40 females in the patient group, and 23 male and 37 female in the control group.

The description table (2) displays key demographic data that were obtained using the self-reported technique and examined as potential risk factors for dementia. These factors included: age, gender, BMI, level of education, smoking, occupation, and marital status, hypertension, and familial AD.

Table (2): Descriptive statistical of the Demographic data of the study population

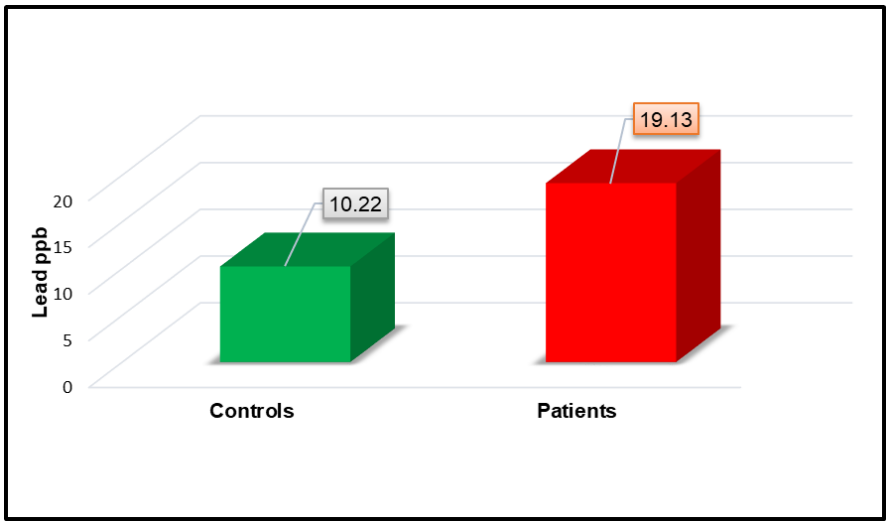
Variable		Patient N= 70	Control N = 60	P Value
Age (Years)	60 - 71 Years	19	28	0.06
	72 - 83 Years	38	26	
	84 - 95 Years	13	6	
Gender	Male	30	23	0.601
	Female	40	37	
BMI Category	Normal Weight	28	27	0.565
	Over Weight	42	33	
Education	Early Childhood	35	22	0.044
	Primary	21	14	
	Bachelor	14	24	
Occupation	Industrial	5	14	0.060
	Others	55	56	
Smoking	Yes	33	26	0.664
	No	37	34	
Marital Status	Married	36	34	0.550
	Single , Widowed, Divorced	34	26	
History Of Hypertension	Yes	34	25	0.431
	No	36	35	
Family AD	Yes	10	4	0.162
	No	50	56	

This study showed there were no significant differences ($P > 0.05$) between dementia and control groups for age, gender, occupation, BMI, marital status, hypertension, and history of familial dementia. Moreover, these two groups differed significantly ($P< 0.05$) in terms of education which is consistent with the study of (23) that indicated that lesser education was related with a bigger modifiable risk factor for AD .

In this study, the risk of lead exposure was calculated by measure the concentration of lead in the serum of AD patients and comparing these values to those of healthy controls. In the group of patients, the highest concentration of lead in the blood was (31.66 ppb) and the lowest concentration was (8.19 ppb).The mean blood Lead levels in our study did not exceed the limit values of 100 ppb(25) . The average values of serum lead levels in the patients was

(19.13±19.11ppb) and (10.22±2.49ppb) in healthy controls . Figure(2). These results showed differences of high statistical significance ($p< 0.001$). In both groups, men had greater serum lead levels than women (16.64 ±22.06ppb) and (13.89±5.84ppb) respectively.

Figure (2): The mean level of lead in studied groups.



Discussion

The results of this study indicate that serum lead concentration is a significant prognostic factor for development of AD. In a cross-sectional investigation, a greater blood lead level was related to worse recall and definition of words, identification of line-drawn objects, and trouble with a perceptual comparison test.(26) Several studies have demonstrated a link between air pollution and dementia. (27) Exposure to lead which has been associated appears to APP metabolic dysregulation, resulting in an increase in app mRNA and Aβ levels, which is a marker of AD, appears to be one of the environmental factors.(28) Through the development of oxidative DNA damage, associations between lead exposure and AD have been thoroughly characterized in molecular investigations. (29) Particularly, oxidative DNA damage has been documented in the brain during the aging process and is a key factor in the etiology of AD.(29) The rise in β-amyloid levels, which results in oxidative damage to the nervous system, may be attributable to oxidative stress caused by lead exposure. (30) Various studies have found a link between Pb exposure and alterations in protein expression and the emergence of clinical markers of neurodegenerative disorders, including Alzheimer's disease. (18) Hypomethylation of a APP gene, a lead-responsive gene, altered genes exposed to lead during early development. In addition, this hypomethylation led to the overexpression of the APP gene and the synthesis of APP protein.(31) Due to the elevated amount of APP caused by lead exposure, the action of the transcription factor Sp1 that regulates AD-related proteins is enhanced. (32) Therefore, Aβ aggregation was stimulated, leading to the development of plaques in the cortex and hippocampus regions of the brain and the activation of apoptosis and autophagy. (33) The observed accumulation of immune-reactive Aβ aggregates within neuronal cells was indicative of the likelihood of AD. (34)

Conclusions

The pathogenesis of AD is linked to elevated lead exposure since the serum lead level is associated with AD. Even though lead is used a lot in industries and the environment around people, poisoning has never been thought of as a possibility.

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Compliance with Ethical Standards

Conflict of Interest

The authors warrant that they don't have any competing interests to declare.

Ethical Approval

All procedures involving human participants in research projects were conducted in compliance with the ethical standard of the research committee of Kerbala University, as well as the 1964 Helsinki declaration and any revisions or other ethical standards deemed equivalent.

Informed Consent

Consent to participate in the study was received from each individual person who took part in the research.

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