American Journal of Alzheimer's Disease & Other Dementias®
2018, Vol. 33(8) 541-547

DOI: 10.1177/1533317518794032
journals.sagepub.com/home/aja

Comparison of Blood Lead Levels in Patients With Alzheimer's Disease and Healthy People

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Abstract

Background: It is argued that breakdown of β-amyloid in the brain causes deposition of senescent plaques and therefore Alzheimer's disease (AD). One of the influential factors for increasing level of this protein is exposure to lead. Our aim was to compare blood lead levels (BLLs) between patients with AD and healthy controls. **Methods:** This case–control study was performed on all patients with cognitive impairment who were referred to the Neurological Clinic of Birjand in 2016 to 2017. Patients were referred to the laboratory for measurement of their serum levels of lead. The controls and patients were matched by age and sex. **Results:** In the AD case group, the average BLL was 22.22 $\pm$ 28.57 μg/dL. Mann-Whitney *U* test showed that BLLs were significantly higher in the patients than in the controls. The unadjusted odds ratio for BLL among the patients was 1.05 (95% confidence interval: 1.01-1.09; $P = .01$) compared to the controls. **Conclusion:** In the present study, BLL was associated with AD.

Keywords
Alzheimer's, blood lead level, Pb, dementia

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease whose symptoms occur in advanced ages although the early stages of the disease occur at an earlier age.[1] Currently, 47 million people across the globe are having dementia that is expected to rise to over 131 million by 2050 as the elderly population is growing.[2] In Iran, it has been estimated that 250 000 to 300 000 people have AD.[3] Alzheimer's disease is associated with profound effects on memory, intelligence, self-care, speech ability, motor activity, landscape recognition, orientation to person, performance, scheduling, and abstract thinking.[4] Due to the gradual deterioration of cognitive functions over time, the patient becomes unable to do his or her daily routines and personal activities and is increasingly dependent on others, which leads to a decrease in self-esteem and development of anxiety and depression.[5]

The main cause of AD is still unknown, but it is argued that genetic and/or hereditary make up, together with environmental factors, can cause intercellular precipitation of a protein called amyloid beta (Aβ) in the brain and thereby constitute causes of the disease.[6] Amyloid β is derived from the amyloid precursor protein (APP). The accumulation of this protein as a plaque in the brain is one of the main characteristics of AD.[7]

Exposure to lead (Pb) appears to be one of the environmental factors for increasing the level of APP and Aβ.[1] Developmental exposure to the heavy metal Pb has been shown to cause both impaired cognition and a latent induction in biomarkers that are related to the amyloid and tau pathways in aging wild-type mice.[8-11] Tau and Aβ have recently been depicted to be involved in some mutual loop correlation, where actions by one affect the other. This study proposes the necessity of tau for Pb

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to change both amyloid and tau-related biomarkers. Tau is similarly needed for Pb, even though partly, to influence the cognitive function and the AD biomarkers.[8]

Lead has been known from ancient times to be an environmental contaminant. After uptake in the human body, the half-life of inorganic Pb is 25 days in blood, 40 days in soft tissues, 7 years in kidneys, and 25 to 32 years in bones.[12,13]

People may be exposed to Pb through paint, glazed utensils, food storage containers that are covered with Pb, car battery covers, and opium consumption. Although organic forms of Pb have been eliminated from gasoline, nonorganic Pb remains a risk to human health.[13-16]

Due to the consumption of high amounts of Pb in the industry and its presence in many areas where people live, this metal is now considered one of the most dangerous environmental pollutants of the world. Lead can enter the body through the digestive system, inhalation, and skin.[13,17-19]

The effects of Pb have been investigated for over 100 years, including effects of Pb on the nervous system. These effects include decreased learning ability, memory loss, reduced neural signaling, and also demyelination and effects on Schwann cells in peripheral nerves as well as presumed accelerated development of AD.[20] Golpayegani and Khanjani noted that heavy metals such as Pb could contribute to developing diseases of the nervous system such as AD.[21] Some studies have determined the association between exposure to Pb and cognitive deterioration in aging humans.[22-24] The Veterans Administration initiated way back in 1963 a prospective longitudinal study, known as the Normative Aging Study (NAS), to investigate the impact of aging on varying health conditions.[25] There has been focus on population subgroups in order to investigate possible associations between cognitive decline and previous nonoccupational exposure to Pb. Several researchers examined the participants in NAS via diverse cognitive tests, sample sizes, and time periods. They propose that greater Pb levels in the blood and the bone or in both correlate with poorer cognitive performance on cognitive tests such as Consortium to Establish a Registry for AD, Wechsler Adult Intelligence Scale-Revised, and Mini-Mental State Examination (MMSE).[23,24,26,27] Significant amounts of Pb have similarly been displayed in the brains of patients with AD.[28] However, biological monitoring of heavy metals in patients with AD has not been sufficiently addressed in the research on the AD pathogenesis. Moreover, little attention has been directed to the potential neurotoxic effects of Pb levels in blood in patients with AD. The half-life of Pb is lower in the blood than in the bones, which is for decades in the latter. Nonetheless, blood lead level (BLL) has been found in a study to significantly predict performance on different measures of speed, memory, and verbal ability.[25] In this same study, both blood and bone (tibia) Pb levels and spatial copying skill correlated meaningfully, and tibia Pb level was significantly associated with pattern memory speed.[26] These associations are in favor of the hypothesis that greater blood and bone Pb levels were significantly correlated with poorer performance on cognitive tests. On the other hand, a large chance of error associated with the measurements of bone Pb when compared to the blood Pb measurements, possibly leading to a lower level of statistical significance. Our aim was, therefore, to compare BLLs between patients with AD and healthy controls to investigate their potential involvement in the pathogenesis of AD.

Methods

In this case–control study, patients with AD, based on National Institute on Aging and the Alzheimer's Association criteria,[29] were selected from the patients referring to the Neurology Clinic of Vali-e-Asr and Imam Reza Hospitals of Birjand, Iran, in 2016 to 2017. The exclusion criteria were having a history of dementia in the family and having other neurologic disorder(s) that could influence cognitive function (eg, severe Parkinson disease) and not volunteering to participate in the study. The research purposes were explained to the patients and their companions, and their consent to participate in the study was obtained. Subsequently, building on convenience sampling method, 27 samples were selected. A total of 54 healthy volunteers who did not have any clinical symptoms indicative on neurologic or psychiatric disease and who were matched with the patients by drug abuse, age, sex, and occupation were assigned to the control group. Blood samples (5 mL) of the participants were collected from the cubital vein and transferred into EDTA-containing tubes. The protocol of this study was reviewed and confirmed by the Ethics Committee of Birjand University of Medical Sciences. The participants or their legal guardians signed a written consent form for blood collection.

The BLL was measured using atomic absorption spectrometry (Varian Co,) according to the National Institute for Occupational Safety and Health protocol. In patients, the severity of the AD was estimated by administering MMSE.[30]

All statistical analyses were performed by using the SPSS version 19. First, data were expressed by descriptive statistics including mean, standard deviation, and frequency. By using the Shapiro-Wilk test, normal distribution of quantitative variables in the 2 groups was investigated. Independent *t* test and analysis of variance were used if the distribution was normal. Otherwise, Mann-Whitney *U* test and Kruskal-Wallis test were used. For qualitative variables, χ^2 or Fisher exact test was used. By using the logistic regression model, the probability of developing AD with respect to BLLs was investigated. $P < .05$ was considered significance level.

Results

The mean age of the participants in case and control groups was 70.85 ± 8.54 and 67.55 ± 6.54 years, respectively. From among the participants, 55.6% were male, and the participants mainly (77.8%) had primary education level. Moreover, 83.9% were involved in nonindustrial occupations, and 28.4% abused drugs. The mean BLL in the case group was 22.22 ± 28.57 μg/dL, and in the control group, it was 7.88 ± 6.63 μg/dL. Nine people in the case group had drug abuse history, and 18 were

Table1. Baseline Characteristics of Patients According to Alzheimer and Healthy Group.

Variable	Total	Alzheimer Group	Healthy Group	Test Result
Age	68.65 ± 7.39	70.85 ± 8.54	67.55 ± 6.54	$t = 1.92$, $P = .07$
Gender				
Male	45 (55.6%)	15 (55.6%)	30 (55.6%)	$P = .59$
Female	36 (44.4%)	12 (44.4%)	24 (44.4%)	
Education				
Primary	63 (77.8%)	23 (85.2%)	40 (74.1%)	$\chi^2 = 2.43$, $P = .30$
Diploma	14 (17.3%)	4 (14.8%)	10 (18.5%)	
Higher bachelor	4 (4.9%)	0 (0.0%)	4 (7.4%)	
Occupation				
Industrial status	13 (16.1%)	2 (7.4%)	11 (20.4%)	$P = .12$
Other	68 (83.9%)	25 (92.6%)	43 (79.6%)	
Addiction				
Yes	23 (28.4%)	9 (33.4%)	14 (25.9%)	$P = .33$
No	58 (71.6%)	18 (66.6%)	40 (74.1%)	

Table2. Comparison of Blood Lead Level Based on Demographic Characteristics in 2 Groups.

Variable	Alzheimer Group	Healthy Group
Age group		
55-65 years	36.8 (3.8-58.5)[a]	4.85 (3.07-7.45)
65-75 years	4.6 (3.6-16.1)	6.70 (4.70-8.10)
Above 75 years	3.3 (2.2-39.3)	5.40 (7.70-8.65)
Test result	$\chi^2 = 3.78$, $P = .15$	$\chi^2 = 3.08$, $P = .21$
Gender		
Male	4.9 (3.8-50.7)	6.70 (4.00-8.10)
Female	4.6 (2.9-31.3)	5.60 (3.52-8.00)
Test result	$z = 0.83$, $P = .43$	$z = 0.85$, $P = .39$
Education		
Primary	7.5 (3.8-50.7)	5.70 (3.95-7.60)
Diploma	2.8 (2.0-3.6)	7.25 (3.60-8.77)
Higher bachelor	–	10.50 (7.30-11.36)
Test result	$z = 5.87$, $P = .01$	$\chi^2 = 2.51$, $P = .28$
Occupation		
Industrial status	51.1 (3.8-51.1)	7.40 (6.77-8.97)
Other	4.8 (3.5-41.9)	5.60 (3.90-7.70)
Test result	$z = 0.78$, $P = .46$	$z = 1.59$, $P = .11$
Addiction		
Yes	54.5 (41.9-78.5)	7.15 (5.20-13.30)
No	3.8 (2.8-5.5)	5.80 (3.90-8.10)
Test result	$z = 3.67$, $P < .001$	$z = 1.53$, $P = .13$

[a]Median (interquartile range); z, test statistics for Mann-Whitney *U* test; χ^2, test statistics χ^2 test.

not drug users. Of the 23 addicted persons in this study, 16 (69.5%) used opium and 7 (30.5%) abused refined opium. Our results showed that there was no significant difference in age, sex, education level, occupation, and substance between the 2 groups (Table 1).

In both groups, the BLLs were higher in men than in women. The BLLs in the patients aged 55 to 65 years, the patients with industrial occupations, and those with drug abuse were higher than others (Table 2). The significantly high BLL values in the 55- to 65 year-olds in individuals with AD stood as the main difference between AD and healthy groups. The AD and healthy individuals of this age-group were similar concerning the parameters of addiction (n = 5 addicted persons per group; $P = .21$) and involvement in industrial occupation (n = 2 persons in the AD and n = 1 in the healthy group; $P = .24$). Thus, these 2 parameters cannot be significant contributors to elevated BLL in this subgroup. Moreover, the age distribution of addiction was not different in the healthy and AD groups ($P > .05$) nor was the duration of addiction ($z = 0.35$, $P = .73$) with the mean durations in the AD and healthy groups being, respectively, 8.84 ± 9.35 and 8.45 ± 8.81 years.

In the case group, the BLLs were significantly higher in the patients with primary education than in the others ($z = 5.87$, $P = .01$). Although the BLL was greater in controls with a bachelor's degree, the difference from other controls was not significant ($\chi^2 = 2.51$, $P = .28$). In the healthy individuals, the median BLL was significantly higher in addicted than nonaddict individuals (54.5 [41.9-78.5] μg/dL vs 3.8 [2.8-5.5] μg/dL; $P < .001$). According to Spearman ρ correlation, there was an insignificant, direct correlation between BLLs and severity of AD ($r = 0.15$, $P = .46$). The mean AD severity in the case group was 18.48 ± 3.78. The results showed that the mean AD severity was higher in men than in women, in the age-group of 55 to 65 years than in the other groups, in patients with high school diploma and higher degrees than in others, in patients with industrial occupations than in those with nonindustrial occupations, and in drug abusers, but the differences were not statistically significant.

Finally, when compared to the control group, the unadjusted odds ratio for BLL in patients with AD was 1.05 (95% confidence interval: 1.01-1.09; $P = .01$).

Discussion

According to the results of this study, BLL is a significant predictor variable for developing AD. To date, no human study has shown a definite relationship between BLL and AD.[31] A few studies in occupational groups have revealed some relationship between Pb exposure and the occurrence of early

symptoms of AD.[32,33] Some studies have shown that tibia Pb level has an association with the prevalence and severity of the white matter lesions in brain magnetic resonance imaging.[34] Wright et al have argued that higher BLLs are associated with increased odds of <24 score on the MMSE, which serves as a conventional cutoff point for an increase in the risk of developing dementia.[24]

With regard to the scores on the MMSE, a prospective study of the older men showed that a one interquartile range increase in cumulative exposure to Pb during lifetime (measured by bone Pb levels) was similar to being 5 years older at baseline.[27] Lead has been shown in a review as a risk factor for neurodegenerative diseases.[35] According to the results of the review, Pb is accumulated in the brain and leaves development-associated effects, which corresponds with the arguments in favor of early environmental basis of neurodegenerative diseases. Reportedly, Pb causes oxidative both stress and neuroinflammation and adjust APP processing and expression; accordingly, the development of neurodegenerative disturbances and AD is enhanced.[35] The association between exposure to Pb and dementia is sensible because of the ability of Pb to cross the blood–brain barrier and its contribution to oxidative stress, neuronal deterioration, and death.[36-38]

Lead is a commonly found neurotoxicant in children. Even for relatively low (subclinical) levels, epidemiologic studies have shown that Pb exposure in childhood influences IQ and social behavior and functioning.[39,40] Subsequent studies have also reported that BLLs even below 10 μg/dL are associated with neurological alterations in children, for example, decline in IQ, exacerbation of attention deficit, hyperactivity disorder, memory loss, and disturbance in academic performance.[41-43] Accumulating toxicological and population-based evidence indicates that cumulative environmental Pb exposure in adulthood is neurotoxic as well.[44] In AD, impaired memory, judgment, attention span, and problem-solving skills are characteristics of the cognitive disability.[35] While the severe cognitive impairments are hallmarks of AD, mild cognitive impairment is widely known to represent a transitional state between dementia and normal aging.[27]

Lead exposure is a major risk factor for accelerated cognition decline.[24,27,36] A review study concluded that cumulative Pb exposure is associated with the decline in the rate of cognitive function in adults.[36] Longitudinal studies have also obtained evidence to support that the Pb-induced decline in cognitive function is more pronounced than changes due to normal aging alone[45] In a cross-sectional study, higher BLL was associated with decreased ability of recalling and defining words and identifying line-drawn objects as well as having difficulty performing a perceptual comparison test.[26] Another review (2014) has reported neurotoxic effects of exposure to Pb in early life.[46] Some studies have shown an association between air pollution and dementia.[47] For example, a study including a prospective cohort of older women in the United States and also investigating neurotoxicological substance inhalation in mice showed the contribution of air pollution particulate matters to induction of neurodegenerative changes and a higher risk of developing AD.[48]

Chen et al studied the association between living near busy roadways and the incidence of dementia, Parkinson disease, and multiple sclerosis in Ontario, Canada, and observed that living near roadways was associated with a higher development of dementia. They proposed that the people living in areas closest to main roads have the highest exposure to leaded petrol.[49] Consistent with the evidence on pollution reported by Chen et al,[49] distance from roadways has been found to be inversely correlated with soil Pb concentrations[36] and human BLL.[27] Molecular epidemiologic studies have shown that cumulative Pb exposure is associated with an increased risk of amyotrophic lateral sclerosis[50-52] and Parkinson disease,[53] suggesting that Pb has remarkable neurotoxic effects.

Some animal studies have shown an association between Pb exposure and Aβ deposits caused by neuropathy in the frontal cortex, which is an indicator of AD.[54,55] A link has also been observed between Pb poisoning and APP metabolic dysregulation, which leads to an increase in APP mRNA and Aβ levels.[37] Studies in rodents have indicated some association of Pb exposure with variations in protein expression and appearance of pathological hallmarks for neurodegenerative diseases, particularly AD.[56,57] Adedayo et al concluded that exposure to Pb induces neuroinflammation and neurodegenerative changes in the medial prefrontal cortex of mice.[58] Also, a review (2016) has proposed the role of selenium as is a Pb-antagonist for improvement in mild cognitive impairment in Alzheimer disease.[59]

Finally, elevated BLLs lead to blood–brain barrier dysfunction, presumably because Pb disturbs the communication between the astrocytes and the endothelial cells. This also contributes to neuronal cell death and induces the inflammatory cascade involving a wide spectrum of chemokines and cytokines. The accompanying cerebral edema can also bring about irreversible brain damages such as decrease in attention and visuomotor reasoning skills and also precipitate asocial behaviors.[60]

Interestingly, we found that the significantly high BLL values in the 55- to 65-year-olds in the individuals with AD explained the main difference between AD and healthy groups. The cases where AD presents before the age of 65 years are generally regarded as early onset. Alongside this, genetic factors can be responsible, particularly AD mutations. Nevertheless, the current data are insufficient to draw firm conclusions on the potential associations between high BLL and early onset of AD.

Limitations

Although we did our best to conduct a well-designed, case–control research, our study has certain limitations including small sample size. Some key factors in patients' lifestyle (eg, diet and socioeconomic status) and exposure to other chemicals were not considered in this study. Therefore, it is difficult to sort out the impact of Pb on AD from other parameters that may

contribute to neurobehavioral measures. In order to generalize results to larger populations, studies with greater number of participants are needed. Further studies on the role of Pb and also of coexposure to other elements and in larger subpopulations are warranted. Moreover, this study investigated associations between BLL and AD. On the other hand, bone Pb levels along with BLL are better predictors of early life Pb exposure and risk of AD.

Conclusions

The BLL is associated with AD. Given the excessive use of Pb in industries and the environments surrounding humans and the possibility of poisoning, more comprehensive studies are needed to determine the definitive relationship between BLL and AD. Because BLLs in opium addicts were higher and with regard to the possibility of Pb poisoning in drug users, investigating the relationship between drug abuse and AD can help develop prevention and treatment programs. Further studies are recommended to investigate the ecological association of geographic regions and elevated Pb exposure with the prevalence of AD.

Acknowledgments

This article was derived from a residency thesis of the first author. The authors sincerely express their gratitude to all patients of the Neurology Clinic of Imam Reza and Vali-e-Asr Hospitals of Birjand. The authors acknowledge the financial support of Birjand University of Medical Sciences for this research project (grant no.: 827).

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The research project of this manuscript was supported financially by Birjand University of Medical Sciences (grant no: 827).

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