OCCUPATIONAL EXPOSURE TO ALUMINUM AND COGNITIVE PERFORMANCE

By

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Abstract

Introduction: As a result of its beneficial properties, Aluminum is widely used in different industrial processes. However, exposure to aluminum in different industries has been linked to many health sides effects, including worker's cognitive performance. **Aim of Work:** early detection of any deviation in cognitive functions for better prognosis among workers exposed to Aluminum. **Materials and Methods:** Analytic cross-sectional study was carried out on sixty-five male workers in the Arab Aluminum Company in Ismailia Governorate. A questionnaire was used to assess socio-demographic data and occupational history. Atomic absorption spectrophotometry was used to asses serum Aluminum level, while Human Elisa Assay was used to measure serum Amyloid Precursor Protein (APP) level. As regard cognitive performance, the Mini Mental State Examination (MMSE) was used. **Results:** The mean ± SD of duration of the current employment among workers was 17.57±10.50 years. The mean ±SD serum concentrations were 2574.23 ± 935.64 pg/ml for APP and 1.156±1.49 mg/l for Aluminum. MMSE scoring mean ±SD was 27.92± 1.78. **Conclusion and Recommendations:** MMSE score and serum Aluminum are negatively correlated. Medical and neuropsychological evaluation, as well as biological monitoring of Aluminum levels of workers should be assessed as pre-employment

medical examination and regularly as periodic testing and compared with the pre-existing findings for appropriate medical interventions.

Keywords: Serum Aluminum, Serum Amyloid Precursor Protein (APP), Cognitive performance and Neuropsychological tests.

Introduction

Aluminum (Al) compounds play an important resource in many industries due to its favorable characteristics, of flexibility, light weight, high conductivity, resistance to corrosion, etc. (Rahimzadeh et al., 2022). In industry, exposure to AL occurs through refining, smelting, welding and its absorption is mainly through inhalation of Al particles in the air (Vlasak et al., 2024).

Now, AL is regarded as a proven neurotoxicant. It may be connected to neurodegenerative conditions like Alzheimer›s disease (AD) (Brough et al., 2020). The role of Al in the etiology of AD is being increasingly supported through many studies. Worldwide, it is perhaps the most prevalent cause of dementia, with an estimated prevalence of 35 million people worldwide. This number will be quadruple by 2050 (Borland et al., 2022).

Alzheimer is a severe neurodegenerative disease characterized by loss of memory and cognitive decline. A mild cognitive impairment is thought to be a prodromal stage of Alzheimer›s disease. The term «Mild Cognitive Impairment» (MCI) was first used to describe the transitional state between normal cognitive function and clinical dementia (Renke et al., 2023).

The deposition of the β-amyloid (Aβ) protein extracellulary is one of the well-defined lesions in AD pathogenesis, with subsequent formation of amyloid plaques and tangles, and selective neuronal loss (Rahimzadeh et al., 2022). Amyloid Precursor Protein (APP) and Aβ buildup in the brain are the primary causes in the start and progression of amyloid genesis in neurodegenerative illnesses. Studies indicated that Al may influence how APP is expressed and processed. Chronic Al exposure causes it to progressively accumulate in different parts of the brain, which is enough to raise APP levels and start the cascade that leads to the development of amyloid plaques (Zawilla et al., 2014).

Currently, clinical and neuropsychological testing are used to diagnose AD (Silvia et al., 2022). One sensitive technique for identifying cognitive impairment is the Mini Mental State Ex-

amination (MMSE), which is frequently employed (Palsetia et al., 2019), but various studies came to various conclusions (Bast-Pettersen, 2022). Serum APP levels may reflect the alterations in cerebrospinal fluid levels seen in AD (Lu et al., 2021). Recently, there has been a greater focus on creating and confirming numerous AD biomarkers as brain imaging, blood and cerebrospinal fluid tests. This novel strategy may encourage early diagnosis and provide a more precise picture of the occurrence and prevalence of AD (Kawahara et al., 2021).

Accordingly, this work was conducted to add to what is known about the relationship between serum Al and serum APP as a potential Al pathway in amyloidogenesis, which could help in screening for early cognitive impairment for better prognosis among Al exposed workers.

Aim of Work

Early detection of any deviation from normal regarding cognitive functions for better prognosis among aluminum exposed workers.

Materials and Methods

Study design: This is an analytic cross-sectional study

Place and duration of the study: The study was conducted in the Arab Aluminum Company in Ismailia Governorate. It is a secondary Al smelter that involves recycling Al products and scrap, with a capacity of 15,000 tons per year during the period from September 2019 to March 2020.

Sample size: In light of the subsequent equation: $n = 2 + [(Z_{a/2} + Z_{b/2} (1-r^2)^{1/2}) / r]^2$, assuming 80% power and 95% level of confidence. For correlation of aluminum serum level with MMSE score, the correlation coefficient r = -0.558 (Moussa et al., 2013). So, n = 30.2 @ 31 subjects. For correlation of serum level of aluminum with that of amyloid precursor protein, the correlation coefficient r = 0.365 (Zawilla et al., 2014). So, n = 58.4 @ 59 subjects. The larger sample size was taken and considering a dropout rate 10%, the final sample size was 65 subjects.

Study sample: Inclusion criteria were literate workers with a minimum of two years of work experience.

Exclusion criteria: include other causes of cognitive functions impairment as history of major head trauma, mental disorders, long-term neurological conditions such stroke,

Parkinson's disease, epilepsy, and intracranial tumors, drug abuse or alcohol intake and family history of Alzheimer disease.

Eligible participants after exclusion criteria constituted our sampling frame (451 workers), from which the required number of participants was selected by the systematic random sampling method.

Study methods: The following was conducted to participants:

- **Questionnaire** including socio-demographic data (age, residence, education level,…etc), occupational (duration of work/years, type of work and use of PPE) and medical histories.
- **Laboratory investigations** for assessment of serum concentration of Aluminum by atomic absorption spectrophotometry and serum Amyloid Precursor Protein (APP) level by Human Elisa Assay.
- **Mini Mental State Examination (MMSE).**

Consent

All participants willingly gave their consent to participate in the study, and they were told that their participation was completely voluntary and that they might decline at any time for any reason. Participants were informed about all results of procedures and tests performed; normal and abnormal. Feedback on the study results was given to the workplace administration.

Ethical Approval

Prior to the study, approval from the administrative authority in the factory was obtained. The study protocol was approved by the Suez Canal University Faculty of Medicine's Ethics Committee (N- 3588). Information was kept confidential.

Data Management

The Statistical Package for Social Science (SPSS) version 20 was used for all statistical analyses. Quantitative data as serum aluminum, amyloid precursor protein concentrations and MMSE scoring were presented as means and standard deviations while percentages were used for qualitative data. To check for normality, the Kolmogorov-Smirnov test was employed. Correlation of serum aluminum, serum amyloid precursor protein levels, and MMSE scoring was tested to detect any significant association. We used multiple linear regression analysis to find the most effective MMSE predictors. Statistical significance was established at $p<0.05$.

Results

Table 1. Workers' distribution based on personal and occupational characteristics (No= 65)

Variables		Frequency	Percentage
Age (years)	20-	5	7.7
	30-	25	38.5
	40-	11	16.9
	50-60	24	36.9
	Mean ± SD	10.46 ± 42.78	
Educational level	Basic	4	6.1
	Vocational	59	90.8
	High	2	3.1
Residence	Rural area	25	38.5
	Urban area	40	61.5
Smoking	Current Smoker	21	32.3
	Ex-smoker	8	12.3
	Non-smoker	36	55.4
Smoking index for current smokers (No=21)	Mean ± SD Range	366.62 ± 232.84 100-900	
Medical history	Diabetics	5	7.7
	Hypertensives	9	13.8
	Heart diseases	4	6.2
Duration of current employment (years)	< 10	20	30.8
	10-	18	27.7
	20-	13	20.0
	30-40	14	21.5
Occupation	Welder	4	6.2
	Quality control	19	29.2
	Smelter	23	35.4
	Polisher	6	9.2
	Maintenance	8	12.3
	Painter	5	7.7

Use of PPE	No PPE	45	69.3
	Mask	11	16.9
	Full shielded mask face	9	13.8
	Respirator	0	00.0

All participants were men. Table 1 showed that the mean ± standard deviation (SD) of workers' age was 42.78±10.46 years. Ninety-eight percent of workers had completed vocational education and 61.5% of them were living in urban areas. The mean ± SD of duration of the current employment among workers was 17.57±10.50 years and the range was 3-35 years. All participants had no relevant other current work outside the company. As regards personnel protective equipment (PPE), 69.3% of workers did not use any. The mask was the most used one (16.9%) followed by the full shielded mask face (13.8%) while respirators were never used.

Table 2. Serum concentrations of Aluminum, Amyloid Precursor Protein and the mini-mental state examination scoring among the studied workers (No =65)

Tests	**Mean ± SD**	**Elevated level No (%)**	**Normal level No (%)**
Serum Al level	1.49± 1.156	54 (83.1)	11 (16.9)
Serum APP level	2574.23 ±935.64	0 (0)	65 (100)
MMSE scoring	28.09± 1.80	0 (0)	65 (100)

AL: Serum concentrations of Aluminum APP: Serum Amyloid Precursor Protein

MMSE: Mini Mental State Examination

Table 2 showed that 83.1% of the studied workers had elevated serum Al level; as regards serum APP level and MMSE scoring were within the normal level.

Table 3. Correlation matrix of serum concentration of Al levels (mg/l), serum APP level (pg/ml), and MMSE score of the studied workers (No=65).

	Aluminum level (mg/l)	APP level (pg/ml)
MMSE score	**-0.410***	-.095
APP level (pg/ml)	-.058	

*: Statistically significant at p- value < 0.01 AL: Serum concentrations of Aluminum
APP: Serum Amyloid Precursor Protein MMSE: Mini Mental State Examination

Spearman Correlation analyses revealed a negative moderate correlation between MMSE scores and serum Al levels (p=0.001). No statistically significant correlations between serum APP levels and either serum Al levels or MMSE scores (Table 3).

Table 4. Correlation between the MMSE scores, serum Al levels, and the employees' age and employment duration (No =65).

	Serum Aluminum levels		MMSE score	
	Correlation coefficient (r)	p value	Correlation Coefficient (r) ¶	p value
Age	0.162	0.197	- 0.295	**0.017***
Employment duration	0.358	**0.003***	-0.417	**0.001***

¶Spearman Correlation MMSE: Mini Mental State Examination *: Statistically significant at p-value < 0.05

A positive weak correlation was found between employment duration and serum AL levels of studied workers (p= 0.003) as shown in Table 4. Additionally, a negative weak correlation between the worker's age and MMSE score (p = 0.017), and a negative moderate correlation between MMSE score and employment duration (p = 0.001) was noticed.

Table 5. Multiple Linear Regression Analysis of the Independent Predictors of MMSE among the studied workers.

	Unstandardized Coefficients		Standardized Coefficients	p Value	95.0% Confidence Interval for B	
	B	Std. Error	Beta		Lower Bound	Upper Bound
(Constant)	29.268	.417		**.000***	28.435	30.102
Serum Al (mg/l)	-.348	.142	-.288	**.017***	-.632	-.065
Duration of employment (yrs.)	-.044	.020	-.257	**.032***	-.084	-.004

R^2= 0.148, Model F (2, 62) = 6.549, p = .003 * : Statistically significant at p <0.05

In multiple linear regression analysis of independent predictors of MMSE (Table 5), the factors entered in the model were age, duration of employment (yrs.), occupation, and serum Aluminum level (mg/l). The best statistically significant independent predictors of MMSE were the duration of employment and serum Al level. The model explains 14.8% of the variance of MMSE.

Discussion

Since aluminum (Al) is known to be neurotoxic, exposure to it at work may impair cognitive function. In the current study, the relationship between workers' cognitive function and occupational exposure to Al were studied. The biological processes of Al uptake and excretion are slow, making Al bio-monitoring methods are acceptable indicators in cases of stable and ongoing exposure (Lu et al., 2021).

The present study revealed that 32.3% of the studied group were smokers and about 90% of them had vocational education (Table 1). A higher percentage was found by Lu and his colleagues in 2021, on their study on longitudinal study of the effects of occupational aluminium exposure on workers ' cognition; they reported that about 70% of their studied group were smokers and 49.6% of workers had less than 9 years education. Years of formal education have an impact on the likelihood of beginning or continuing to smoke. Higher educated people quit from smoking because they are more likely to be aware of the negative effects of smoking as well as the advantages of quitting.

According to the current study, 83.1% of the workers under investigation had increased serum Al levels (Table 2). This was in line with the study done by Kieswetter and his colleagues in 2007 who stated that workers exposed to Al for a prolong period had a high level of serum Al.

There was a significant negative correlation between serum Al and MMSE scores, but no statistically significant correlations between APP levels and either serum Al nor MMSE scores among the studied group (Table 3). Numerous studies showed that people who were exposed to Al, either through their jobs or the environment, scored poorly on the MMSE (Gowda et al., 2019management, and particularly legal issues. Materials and Methods: We conducted a retrospective chart review using a structured data-extraction tool. A total of 23 female forensic inpatients were admitted under the Department of Psychiatry from January 2006 to June 2016. Data were analyzed by descriptive statistics. Results: The mean age of the patients was 31.3 ± 7.9 years. In total, 82.6% of them were married, 87% were from a nuclear family, and 78.3% were from an urban background. Totally, 73.9% were referred from prison and 26.1%

from the court. However, 73.9% were referred for the purpose of diagnosis and treatment and 21.7% for assessment of fitness to stand trial. Moreover, 47.8% had an alleged charge of murder (of killing close family members, Xu et al., 2021management, and particularly legal issues. Materials and Methods: We conducted a retrospective chart review using a structured data-extraction tool. A total of 23 female forensic inpatients were admitted under the Department of Psychiatry from January 2006 to June 2016. Data were analyzed by descriptive statistics. Results: The mean age of the patients was 31.3 ± 7.9 years. In total, 82.6% of them were married, 87% were from a nuclear family, and 78.3% were from an urban background. Totally, 73.9% were referred from prison and 26.1% from the court. However, 73.9% were referred for the purpose of diagnosis and treatment and 21.7% for assessment of fitness to stand trial. Moreover, 47.8% had an alleged charge of murder (of killing close family members and Bast-Pettersen, 2022). Based on studies conducted on 1353 Canadian uranium and gold miners, neuropsychological testing revealed that a relative risk of 2.6 meant that a significantly higher proportion of miners exposed to AL than those not exposed experienced cognitive impairment (Zarnke et al, 2022). On the same line, in Italy, a case-control study conducted by Polizzi and his colleagues, 2002, on 64 former Al dust-exposed workers reported a negative correlation between MMSE scores and serum Al.

Furthermore, in a study involving 70 unexposed Chinese controls and 66 retired Al pot-room workers, the mean serum Al of the Al-exposed workers (25.18 ± 2.65 μg/L) was significantly greater than that of the controls (9.97 ± 2.83 μg/L) ($p < 0.01$). The group exposed to Al had a significantly lower overall MMSE score (26.13± 2.57) compared to the control group (27.89± 1.91) ($p<0.01$) (Lu et al., 2014). The findings of Lu et al., 2014 can result from the extended period of Al exposure.

The normal mean value for MMSE despite the high mean serum concentrations of Al among the studied workers (Table 2) could be attributed to a number of factors such as the different forms of Al exposure and duration of current employment as 30.8% of workers has less than 10 years in their work (Table1).

A statistically significant positive weak correlation was detected between serum Al levels and employment

duration; yet, no correlation could be found between serum Al levels and worker's age (Table 4). The origin of this conflict could be explained by the finding that although the mean age of the studied workers was 42.78 ± 10.46 years, 38.5% of workers aged less than 40 years (Table1).

In multiple linear regression analysis of independent predictors of MMSE (Table 5), the best statistically significant ones were the duration of employment and serum Al level. Yet no causal relationship could be detected as the design of the current study is cross-sectional. The majority of neuro-toxicological studies were on low-level exposure, therefore the reported impairments are frequently mild since they represent marginal or subclinical changes (Bast-Pettersen, 2022).

In the same line, a meta-analysis study examine the relationship between long-term Al exposure and Alzheimer's disease risk found that Al -exposed workers had an overall statistically significant decline in MMSE (Vlasak et al., 2024).

Unlike the current study's findings, a meta-analysis study published in 2015 by Virk and Eslick, which quantify the relationship between workplace exposure to Al and risk of AD which noticed that there were three case-control studies totaling 1,056 participants. The analysis's findings showed that occupational exposure to Al did not correlate with AD (95% confidence interval: 0.59–1.68, Odds Ratio: 1). The authors came to the conclusion that their data did not support that Al having a causal involvement in the etiology of AD. But they also said that a role for Al cannot be definitively excluded in the absence of prospective studies with more precise ascertainment of exposure.

There is strong evidence to suggest that Al plays a key role in amyloidgenesis, which is the process by which amyloid plaques are formed (Gupta et al., 2005). Studies indicate that Al might control how APP was expressed and processed. In fact, prolonged oral consumption of Al caused APP levels to rise and set off the chain reaction that led to the development of brain amyloid plaques (Nadiga et al., 2024). Walton and Wang observed that long-term exposure to dietary Al at levels relevant to humans resulted in the up-regulation of APP expression in brain regions. Early in the series of events that cause amyloid plaque formation in the human brain,

neurological diseases to appear, and those conditions to progress, there is up-regulated expression of APP (Walton and Wang, 2009). Serum APP levels were normal among all the studied workers (Table 2). Moreover, there was no correlation between serum Al and serum APP level (Table 3). These results oppose the usefulness of serum APP for early Al neurotoxicity identification in exposed workers. This discrepancy could originate from different routes of exposure to Al, dietary versus occupational exposure.

Zawilla and her colleagues in 2014 conducted a study in an Aluminum factory on fifty-four exposed workers and fifty-one matched controls and found a significant high level of serum Al among the exposed workers associated with increase in serum APP levels. APP significantly and positively correlated with serum Al. On the Addenbrooke's Cognitive test, the exposed workers performed poorly, but there was no discernible relationship between the test's overall score and APP. They came to the conclusion that cognitive impairment is linked to occupational exposure to Al. Their results, however, contradict the usefulness of serum APP as a screening indicator for cognitive impairment (Zawilla et al., 2014).

Polizzi et al. , 2002, reported that with age, Transferrin receptor-mediated endocytosis allows aluminum to pass the blood-brain barrier and accumulate in brain tissues. This explain the individual susceptibility to AL poisoning64 former aluminium dust-exposed workers were compared with 32 unexposed controls from other companies matched for age, professional training, economic status, educational and clinical features. The findings lead the authors to suggest a possible role of the inhalation of aluminium dust in pre-clinical mild cognitive disorder which might prelude Alzheimer's disease (AD. The discrepancy between the previous studies and the findings of the current study could be related to the stage and the progress of the toxicity; thus, APP abnormalities of metabolism in relation to Al exposure could be identified in well-established disease in moderate to severe stage and not in the early stages as the condition of the current study.

So, the theory that exposure to Al in industry, is associated with impairment of cognitive functions discussed throughout the literature is further confirmed by the results the current study and chronic Al exposure can

cause cognitive impairment. However, serum amyloid precursor protein does not seem to be involved in the cognitive deficit linked to Al exposure.

Conclusion

About 83% of the studied workers had elevated serum Al levels while MMSE scores and serum APP are normal. MMSE scoring and Al blood level are negatively correlated. Multivariate analysis showed that the best predictors of MMSE are the employment duration and serum Al. Therefore, cognitive function impairment is linked to occupational exposure to Al.

Recommendations

Our study findings highlighted the potential impact of aluminum exposure on workers, this may provide the factory a reference to formulate employee health measures. Accurate medical and neuropsychological evaluation, as well as biological monitoring of Aluminum levels of workers should be assessed as pre-employment medical examination and regularly as periodic testing and compared with the pre-existing findings for appropriate medical interventions and documentation of progress.

The availability and the efficacy of the currently used personal protective equipment should be assessed regularly. Precautions concerning proper maintenance and storage of personal protective equipment should be followed. Health education and training programs should be provided for workers regarding the proper usage of personal protective equipment. Also, the applied control measures should be assessed regularly.

Conflict of Interest

Authors have declared that no conflict of interest exists.

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