Letter to the Editor

Cognitive Status of Electrolytic Aluminum Workers: A Cross-sectional Study Using Cognitive Screening Tests*

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In 2014, a case of a worker diagnosed with Alzheimer's disease (AD) following occupational exposure to aluminum (Al) was first reported by British scientist Christopher Exley[1]. This patient had an early onset and a shorter course than the average person, indicating that Al may be an important environmental factor resulting in cognitive impairment.

For occupational workers, Al enters mainly through the respiratory tract. Furthermore, Al^{3+} enters the brain through the blood-brain barrier or olfactory bulb directly and produces severe neurotoxicity[2].

Most previous research have focused on secondary Al processing among smelter and foundry workers, and emphasized little on primary Al production. More than half of the world's electrolytic Al is produced in China. Workers are highly exposed to Al oxide dust that has a bioavailability 7 times higher than drinking water[3]. Research on the cognitive assessment of electrolytic Al workers is lacking in China.

In this case, the first complaint was memory impairment (AD's core symptom). Were there damages in other cognitive domains that have gone unnoticed? As we know, cognition includes various domains such as orientation, memory, language, visuospatial and executive ability, attention, calculation, and comprehension. The relationship between Al and cognitive domains is uncertain. Given the early onset and mild symptoms, early detection of impaired domains and separation from Al becomes necessary.

All participants (30–59 years) were from different department of the SH Aluminum factory, China. One group included 172 electrolytic Al workers. The control group included 245 transport workers without any history of Al exposure. The two groups were matched in age and education. All workers were male and wore work clothes, masks, and gloves during working time. Al concentration in drinking water was lower than national standards (< 0.2 mg/L). Accurate demographic and medical information was collected. Cognitive functions were evaluated using Cognitive Screening Tests, including the Mini-mental state examination (MMSE), Clock drawing test (CDT), Digit span test (DS), Fuld object-memory evaluation (FOM), and Verbal fluency Test (VFT). (Supplementary File, available in www.besjournal.com).

Exclusion criteria for our study were: (1) any diseases that may cause cognitive impairment including hepatic or renal disorders, brain trauma, hypertension, diabetes, cerebrovascular disease, epilepsy, Parkinson's, and mental diseases; (2) any family history of dementia in first-degree relatives; (3) any history of regular drug use (anti-acid drugs containing Al or mental drugs affecting the central nervous system); (4) apparent poor vision and hearing; (5) absence of intact demographic information and blood samples.

All participants signed informed consent. The Ethics and Human committees of Shanxi Medical University approved the study. Face-to-face interviews and cognitive assessments were performed on the same day.

Venous blood was collected in EDTA tubes from each participant. The plasma was separated within 30 min by centrifugation (4 °C, 5 min, 402 g/min) and stored at −80 °C until analysis. Plasma Al was analyzed by inductively coupled plasma mass spectrometry (ICP-MS) (NexlON 300D, PekinElme, USA). Each sample was measured twice. The instrument was calibrated after every 10 samples, using the Al standard liquid (Agilent, USA). The linearity, limit of detection (LOD), and recovery rates

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were 0.9998−1, 0.39 μg/L, and 98.24%−99.65%, respectively. Results lower than LOD were expressed by LOD/2.

Education was classified into junior middle school and below (≤ 9 years) and senior middle and above (> 9 years). Marital status and household incomes per capita were dichotomized into no or yes and < 1,000 or ≥ 1,000 Yuan per month, respectively. Smokers were defined as participants who smoked during the investigation or had quit smoking for less than 6 months. The participants who drank during the investigation or had quit drinking for less than 6 months (more than once a week) were defined as drinkers. Plasma Al was categorized into a binary variable according to the median. Two chief cognitive domains were identified after combining the tests: 'learning and memory ability' including 'recall in MMSE' + FOM (total retrieval) + DSF, and 'visuospatial and executive ability' including 'visuospatial in MMSE' + CDT + DSB[4]. The cut-off of various tests (MMSE/CDT/DS/FOM) and cognitive domains were 1 standard deviation below the mean of the controls[5].

SPSS 22.0 was used for analysis. The Student's *t*-test or Mann-Whitney U test was used to compare continuous variables depending on the distribution types. Differences between categorical variables were calculated using the chi-square test. Multivariate logistic regression was used to analyze all the risk factors. A P value < 0.05 was considered statistically significant.

Table 1 presents the characteristics of electrolytic Al workers and controls. Age, education, marriage, income, and smoking between the two groups were adjusted and compare (P > 0.05). The electrolytic Al workers had a lower drinking proportion (P < 0.001). There was a significant difference in plasma Al between the two groups (P < 0.001) with the

Table 1. Basic information of electrolytic Al workers and controls

Variables	Electrolytic Al workers (*n* = 172)	Controls (*n* = 245)	*P* value
Age(y), mean ± SD	40.89 ± 5.77	41.63 ± 5.38	0.181[a]
Education, *n* (%)			
Junior middle and below	115 (66.9)	175 (71.4)	0.187[b]
Senior middle and above	57 (33.1)	70 (28.6)	
Marriage, *n* (%)			
No	1 (0.6)	2 (0.8)	0.780[b]
Yes	171 (99.4)	243 (99.2)	
Income, *n* (%)			
< 1,000 RMB	46 (27.7)	77 (31,4)	0.419[b]
≥ 1,000 RMB	120 (72.3)	168 (68.6)	
Smoking, *n* (%)			
No	53 (30.8)	82 (33.5)	0.742[b]
Yes	119 (69.2)	163 (66.5)	
Drinking, *n* (%)			
No	141 (82.0)	164 (66.9)	0.001[b]
Yes	31 (18.0)	81 (33.1)	
Plasma Al, Med (25^{th}–75^{th})	21.18 (11.84, 40.54)	10.46 (5.32, 19.24)	< 0.001[c]
Plasma Al, *n* (%)			
< 14.90 μg/L	55 (32.0)	153 (62.4)	< 0.001[b]
≥ 14.90 μg/L	117 (68.0)	92 (37.8)	
Al working time, mean ± SD	6.64 ± 6.37	0	< 0.001[a]

Note. Concentration unit of plasma Al is μg/L. Data were presented as Mean (SD) or *n* (%) or Med (25^{th}–75^{th}). [a]*P* value determined by Student's *t*-test; [b]*P* value determined by Pearson chi-square test; [c]*P* value determined by Mann-Whitney *U* test. Missing value: Al exposure workers--income (6). RMB is Chinese money.

proportion of plasma Al ≥ 14.90 μg/L being significantly higher in Al workers than in controls ($P < 0.001$).

Table 2 presents the cognitive status of the groups. Electrolytic Al workers had low scores in MMSE, CDT, DS, and FOM ($P < 0.001$). In MMSE, there were significant differences in recall ($P = 0.035$) and visuospatial domains ($P = 0.014$). In the CDT, H-position error was found to be the most common participant error type. C-distortion, H-position, and H-perseveration were significantly different between the two groups ($P = 0.037$, $P = 0.013$, $P = 0.029$). The Supplementary Figure S1 (available in www.besjournal.com) displays several typical error types of Al workers. Al workers also had low DS and FOM scores ($P < 0.01$).

Supplementary Table S1 (available in www. besjournal.com) presents comparisons in the plasma Al between the cognitive impairment group and the normal group. Plasma Al was elevated in the cognitive impairment group ($P < 0.05$).

We found that the higher level of plasma Al was

Table 2. The cognition of workers in two groups

Variables	Electrolytic Al workers (*n* = 172)	Controls (*n* = 245)	*P* value
MMSE, mean ± SD	27.93 ± 1.91	28.62 ± 1.25	< 0.001[a]
Orientation	9.93 ± 0.30	9.98 ± 0.18	0.054[a]
Registration	2.97 ± 0.25	3.00 ± 0.00	0.072[a]
Recall	2.27 ± 0.99	2.45 ± 0.71	0.035[a]
Attention and Calculation	4.48 ± 1.01	4.64 ± 0.70	0.057[a]
Language	7.54 ± 0.57	7.65 ± 0.82	0.122[a]
Visuospatial ability	0.74 ± 0.44	0.84 ± 0.37	0.014[a]
CDT, mean ± SD	2.70 ± 1.03	3.16 ± 0.86	< 0.001[a]
Error type of CDT, *n* (%)			
C-distortion	9 (5.2)	4 (1.6)	0.037[b]
N-position	22 (12.8)	18 (7.3)	0.063[b]
N-omission	11 (6.4)	14 (5.7)	0.773[b]
N-perseveration	6 (3.5)	14 (5.7)	0.295[b]
N-reversal	1 (0.6)	2 (0.8)	0.780[b]
H-position	102 (59.3)	115 (46.9)	0.013[b]
H-omission	8 (4.7)	4 (1.6)	0.070[b]
H-perseveration	21 (12.2)	15 (6.1)	0.029[b]
H-reversal	0 (0)	1 (0.4)	0.402[b]
H-code	1 (0.6)	0 (0)	0.232[b]
DS, mean ± SD	10.97 ± 1.96	12.24 ± 2.15	< 0.001[a]
Forward	6.81 ± 1.25	7.59 ± 1.32	0.001[a]
Backward	4.16 ± 1.09	4.65 ± 1.28	< 0.001[a]
FOM, mean ± SD	23.60 ± 3.12	25.80 ± 2.84	< 0.001[a]
Total retrieval (0–30)	23.60 ± 3.12	25.80 ± 2.84	< 0.001[a]
Total storage (0–30)	25.96 ± 2.68	27.39 ± 2.40	< 0.001[a]
Repeated retrieval (0–20)	13.08 ± 2.95	15.21 ± 2.94	< 0.001[a]
Infective reminder (0–20)	1.34 ± 1.62	0.78 ± 1.48	< 0.001[a]
Verbal Fluency Test	33.91 ± 8.53	38.66 ± 8.22	0.002[a]

Note. Data were presented as Mean ± SD. [a]*P* value determined by Student's *t*-test; [b]*P* value determined by Pearson chi-square test. C-circle, N-number; H-hand.

associated with a high risk of cognitive impairment in CDT (*OR*: 1.790, 95% *CI*: 1.127, 2.843, *P* = 0.014) (Supplementary Table S2, available in www. besjournal.com). Furthermore, we analyzed the relationship between plasma Al and specific cognitive domains (learning and memory ability; visuospatial and executive ability) presented in Table 3. After adjusting the age, education, income, smoking, and drinking, the elevated plasma Al was found to increase the risk of learning and memory impairments (*OR*: 1.883, 95% *CI*: 1.203, 2.947, *P* = 0.006) as well as visuospatial and executive dysfunction (*OR*: 2.016, 95% *CI*: 1.111, 3.656, *P* = 0.021).

In our study, the workers' average occupational exposure to Al was 6.64 years. Our findings showed no significant differences in age, education, income, marriage, and smoking between the two groups. Controls had a higher drinking ratio. However, Al workers had higher plasma Al level than controls. In previous occupational studies[6,7], the median of plasma Al varied in the range of 9.9−33.5 μg/L. Our result (21.18 μg/L) was within this range. The plasma Al level in the control group was higher than the general population (< 5 μg/L), probably because the control group also lived in the Al plant community, which was already polluted.

We utilized cognitive screening tests including MMSE, CDT, DS, FOM, and VFT, to evaluate the participants' cognitive status. In MMSE, there were statistical differences in recall and visuospatial ability. In our previous study[8], orientation, recall, and calculation ability were decreased in Al retired workers. The cause of this difference may be the comparatively younger age and higher education level of the participants, with possibly better orientation and calculation ability.

Age was also a risk factor. However, the relationship between income and cognition was controversial. High income may be a protective factor, but our workers' income levels were low and did not reflect the advantages of income. Smoking and drinking were unrelated to cognition in our study. The neurotoxicity of Al was also confirmed by Polizzi[9], Zawilla[7], and other scholars. In contrast, several studies[10,11] found no association between Al exposure and cognition. Despite this, the role of Al cannot be definitively excluded.

The influence of Al on 'learning and memory ability' was confirmed by many previous researchers. 'Visuospatial and executive ability' was also significantly affected by Al. In Zawilla's study[7], memory, language, and visuospatial abilities of Al workers were impaired, but the data of a multivariate analysis were lacking. In recent years, visual space and imaging have been increasingly researched. MRI studies have identified the relation of CDT impairment to temporoparietal regions.

Table 3. Multivariate logistic regression of cognitive domains

Variables	A*OR* (95% *CI*)	*P*-value
Memory and learning		
Age	1.006 (0.966, 1.047)	0.777
Education	0.986 (0.605, 1.606)	0.954
Median of Al	1.883 (1.203, 2.947)	0.006
Income	0.719 (0.447, 1.158)	0.175
Smoking	0.785 (0.492, 1.254)	0.312
Drinking	0.668 (0.390, 1.145)	0.142
Visuospatial and executive ability		
Age	1.044 (0.992, 1.098)	0.097
Education	1.434 (0.797, 2.580)	0.230
Median of Al	2.016 (1.111, 3.656)	0.021
Income	0.936 (0.508, 1.725)	0.831
Smoking	1.157 (0.630, 2.126)	0.638
Drinking	0.797 (0.410, 1.551)	0.505

Note. *OR* is adjusted by age, education, smoking, drinking and income. Cut-off is 1 standard deviation below the mean of the control.

Matsuoka[12] found that CDT scores were positively correlated with regional gray matter volume in the bilateral posterior temporal lobes, right posterior inferior temporal lobe, and right posterior superior temporal lobe, based on different scoring methods. Hirjak[13] suggested the involvement of different hippocampal subfields in impaired CDT performance. We speculate that the hippocampus and temporoparietal areas of Al workers may be affected.

For the relationship between Al and cognition, epidemiological studies can only provide uncertain data; the specific pathogenesis needs further study. We will conduct magnetic resonance research on Al workers. There were some limitations in our study. First, all workers were exposed to Al from only one factory. Second, there was no imaging data to further explain the impairments. Last, a longitudinal follow-up study is needed to clarify the hazards of Al.

The cognitive functions of electrolytic Al workers declined. Learning and memory ability, as well as visuospatial and executive ability, were affected.

The authors declare no conflicts of interest.

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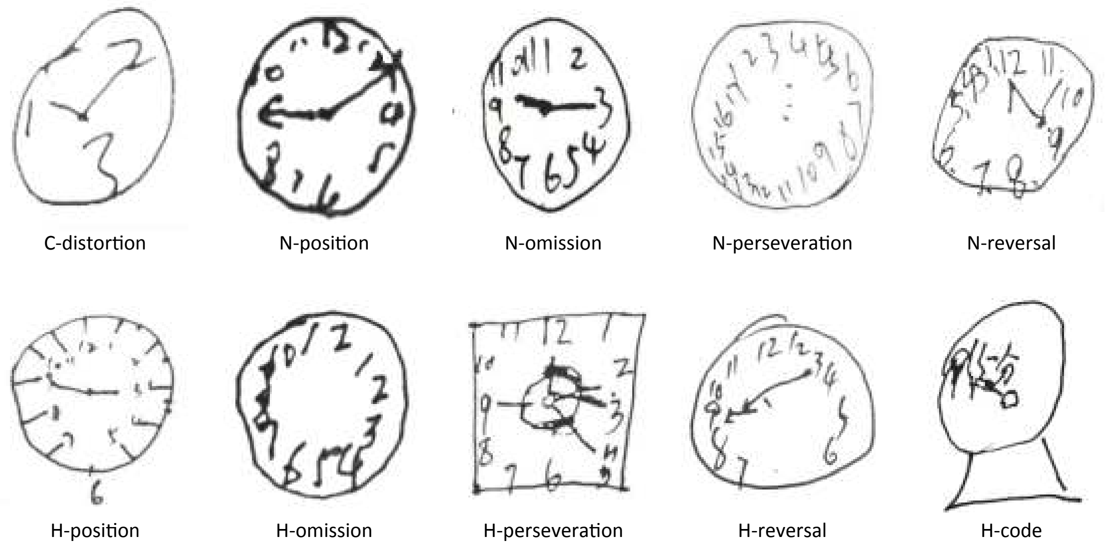


Supplementary Figure S1. Various error types among electrolytic Al workers.

Supplementary Table S1. The plasma Al between cognitive impairment group and normal group

Variables	The plasma Al of abnormal	The plasma Al of normal	*P* value
MMSE	17.14 (8.73, 29.52)	13.74 (6.78, 24.12)	0.020
CDT	18.10 (8.88, 31.00)	13.05 (6.63, 23.16)	0.004
DS	16.10 (8.09, 30.22)	13.71 (6.65, 23.69)	0.046
FOM	18.97 (7.71, 37.49)	13.72 (6.94, 23.12)	0.009

Note. Concentration unit of plasma Al is μg/L. Data were presented as Med (25^{th}–75^{th}). *P* value determined by Mann-Whitney U test. Cut-off is 1 standard deviation below the mean of the control.

Supplementary Table S2. Multivariate logistic regression of cognitive impairment

Variables	MCI, *n* (%)	AOR (95% *CI*)	*P* value
MMSE	417 (19.7)		
Age		1.062 (1.015–1.113)	0.010
Income		1.886 (1.032–3.447)	0.039
CDT	417 (24.9)		
Median of Al		1.790 (1.127–2.843)	0.014
DS	414 (30.0)		
Age		1.067 (1.025–1.110)	0.002
FOM	415 (18.5)		
Income		0.593 (0.356, 0.988)	0.045

Note. *OR* is adjusted by age, education, smoking, drinking, income. A*OR*: adjusted odds ratio cut-off is 1 standard deviation below the mean of the control.

Supplementary file

Employee health survey form

Part 1: Basic information

1. Name________
2. Gender________ ①man ②woman
3. Birthday________(YY/MM/DD)
4. Marriage________ ①unmarried ②married
5. Ethics________ ①Han Chinese ②non Han Chinese
6. Tel________
7. ID________
8. Income________①<1000 yuan per month per person ②≥1000 yuan per month per person
9. Education ____years ①illiteracy ②primary school ③junior high school ④senior high school ⑤college
10. Occupational history

    The first job______ time_______ protection_____________

    The second job___ time_______ protection_____________

    The third job_____ time_______ protection_____________

    The forth job_____ time_______ protection_____________
11. Smoking_______ ①No ②Yes, _____cigarettes/day, ___years, quit _____①No ②Yes
12. Drinking_______ ①No ②Yes, _____ml/day, ___years, quit _____①No ②Yes

    How often you eat vermicelli or Fritters? _____________
13. Do you use aluminum cookware in your home? ①No ②Yes
14. Do you take a medication for 3 consecutive months? ①No ②Yes drug name_____________

Part 2: Medical information

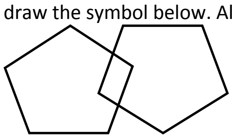
1. Past history: hypertension, diabetes mellitus, thyroid disease, cerebral trauma, cardiovascular diseases, stroke, mental diseases, anemia
2. Family history

    Disease: 1._______2._______3._______

    Relationship with participant: 1._______2._______3._______
3. Participant attitude 1. Serious 2. Not serious

Part 3: Cognitive evaluation

Supplementary Table S3. Mini-Mental State Examination (MMSE)

Maximum score	Patient's score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens."(93, 86, 79, 72, 65, …)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase:'rui xue zhao feng nian'"
3		"Take the paper in your right hand, fold it in half, and put it on the left leg." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Clock drawing tests (CDT)

"Please draw a clock face, and place all the numbers on it. Then set the time at 15 past 9."

Supplementary Table S4. Digital span

Forward		Backward	
5-8-2	6-9-4	2-4	5-8
6-4-3-9	7-2-8-6	6-2-9	4-1-5
4-2-7-3-1	7-5-8-3-6	3-2-7-9	4-9-6-8
6-1-9-4-7-3	3-9-2-4-8-7	1-5-2-8-6	6-1-8-4-3
5-9-1-7-4-2-8	4-1-7-9-3-8-6	5-3-9-4-1-8	7-2-4-8-5-6
5-8-1-9-2-6-4-7	3-8-2-9-5-1-7-4	8-1-2-9-3-6-5	4-7-3-9-1-2-8
2-7-5-8-6-2-5-8-6	7-1-3-9-4-2-5-6-8	9-4-3-7-6-2-5-8	7-2-8-1-9-6-5-3
5-2-7-4-9-1-3-7-4-6	4-7-2-5-9-1-6-2-5-3	6-3-1-9-4-3-6-5-8	9-4-1-5-3-8-5-7-2
4-1-6-3-8-2-4-6-3-5-9	3-6-1-4-9-7-5-1-4-2-7	6-4-5-2-6-7-9-3-8-6	5-1-6-2-7-4-3-8-5-9
7-4-9-6-1-3-5-9-6-8-2-5	6-9-4-7-1-9-7-4-2-5-9-2		

Supplementary Table S5. Fuld object-memory examination (FOM) and Rapid Verbal Retrieve (RVR)

	tactile naming	Visual naming	1st recall	2nd recall	3rd recall	number	animal	vegetable	fruit
Ball									
Bottle									
Key									
scissor									
card									
ring									
spoon									
cup									
button									
paper clip									

Scale index:

Mini-mental state examination (MMSE) MMSE, is widely used in clinical and epidemiological fields. It is a global measurement for cognition: orientation in time and place, memory, language, calculation and constructional praxis. The scores range from 0 (worst) to 30 (best).

Clock drawing test (CDT) CDT is the second widely used screening tool for cognition detection (Langa KM,2017). It is simple and easy to use, especially suitable for epidemiological investigations. However, it is a complex task to evaluate visuospatial skills and executive function. "Please draw a clock face, and place all the numbers on it. Then set the time at 15 past 9." Here we adopt the "4-point scoring system" from 0 (worst) to 4 (best). Error types of CDT were categorized into circle (C), numbers (N) and hands (H). The following types were analyzed: circle shape (C-distortion), numbers or hands positions (N/H-position), lack of numbers or hands (N/H-omission), more or repeated numbers or more than two hands (N/H-perseveration), numbers or hands reversal (N/H-reversal), writing the digital time (H-code)[1].

Digit span test (DS) DS is an additional neurocognitive measure[2] to measure short-term memory and working memory of the participants. The forward digit span (0-12) assesses immediate memory of the number sequence and the backward digit span (0-10) reflects mind executive ability.

Fuld objective memory evaluation (FOM) and Verbal Fluency Test (VFT) FOM is a screening tool to assess learning, memory and selective-reminding procedures[3]. Ten common objects (e.g. ball, spoon, key) were put in a black bag for tactile naming. After identification, the participant was asked to recall these objects within 60s, the missing objects would be told. VFT (vegetables, fruits, animals) was interspersed in the test. Therefore, this was a retrieval-reminding-distraction progress. For the sake of time, we conducted 3 recalls without delayed recall. The information of total retrieval (TR, 0-30), total storage (TS, 0-30), repeated retrieval (0-20) and ineffective reminders (0-20) was collected[4-9].

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