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Oxidative Stress Markers and Metal Ions are Correlated With Cognitive Function in Alzheimer's Disease

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Abstract

We investigated oxidative stress markers and metal ions in patients with Alzheimer's disease (AD). The serum levels of ceruloplasmin (CER), C-reactive protein (CRP), uric acid (UA), homocysteine (Hcy), copper, iron, and zinc were determined in 125 patients with AD (mild, n = 2 8; moderate, n = 42; and severe, n = 55) and 40 healthy control (HC) participants. Compared to HC, CER and UA levels were significantly lower in moderate and severe AD groups, whereas CRP and Hcy levels were significantly higher in the severe AD group. Copper level was significantly higher in moderate and severe AD groups than the other groups. Compared to HC, iron level was significantly higher in patients with AD, whereas zinc level was significantly lower in patients with AD. In patients with AD, the severity of cognitive impairment was positively correlated with CER, UA, and zinc levels, whereas it was negatively correlated with copper level. Taken together, our findings provide a novel approach to assess AD progression.

Keywords

Alzheimer's disease, dementia, oxidative stress markers, metallic ions

Introduction

Alzheimer's disease (AD) is the most common cause of senile dementia and is usually characterized by progressive cognitive degeneration, visuospatial memory dysfunction, and eventual death.[1] Senile plaques, neurofibrillary tangles, granulovacuolar degeneration in the hippocampus, and a decrease in the number of cerebral neurons are among the pathological hallmarks of AD.[1-3] In China, AD accounts for around 50% of the senile dementia cases, with a morbidity rate of 6.6% among the elderly (>65 years of age) population.[4]

Accumulating evidence suggests a correlation between AD and serum oxidative stress (OS) markers.[5] Ceruloplasmin (CER) is a copper-containing α2-glycoprotein produced by the liver. Ceruloplasmin has antioxidant properties, and it is essential for copper-transportation and iron metabolism.[6] Uric acid (UA) is an end product of purine metabolism that plays an important role in scavenging free radicals.[7] Their antioxidant function influences neurotransmitter synthesis and the induction of neuronal lesions.[6] C-reactive protein (CRP) is an acute-phase protein that increases upon the exposure to OS.[8] Hyperhomocysteinemia could accelerate the progress of AD by inducing cerebrovascular lesions through chronic OS.[9] Furthermore, several metallic ions are also closely associated with inflammation and OS in neuronal disorders including dementia.[10] However, the relationships between the severity of dementia and serum levels of OS markers and metal ions remain to be elucidated.[9]

Therefore, in this study, we investigated correlations between CER, UA, CRP, and homocysteine (Hcy) serum levels and AD disease severity, as well as the serum levels of metallic ions and disease severity in patients with AD with varying degrees of disease severity as well as a control group of healthy elderly individuals.

Methods

Patients

From March 2013 to March 2015, a total of 125 inpatients and outpatients with AD were enrolled from the neurological and/or psychiatric departments of Kangci Hospital, Jiaxing; The Second Hospital, Jiaxing; and Tongde Hospital, Zhejiang.

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The Second Hospital as well as Kangci and Tongde Hospitals are top-level medical facilities in China, and AD diagnosis was based on the latest diagnostic criteria released by the US National Institute of Aging and the Alzheimer's Association.

The exclusion criteria included patients with schizophrenia history, severe depression, and/or anxiety; patients diagnosed with Parkinson disease, frontotemporal dementia, and/or Huntington disease; patients with cerebrovascular diseases; patients presented with cognitive dysfunction due to other etiologies, including trauma to the central nervous system (CNS), tumors, infections, metabolic diseases, and normal pressure cranial hydrocephalus; folic acid and vitamin B_{12} deficiencies, hypothyroidism, alcohol dependence, and Korsakoff syndrome; aphasia or disorders of consciousness affecting cognitive tests; patients with cardiovascular diseases, including severe arrhythmia (heart rate >120 or <50 bmp), myocardial infarction within the previous 6 months, and other coronary heart diseases conditions, acute or chronic heart failure, severe or resistant hypertension, viral myocarditis, primary cardiac myopathy, and severe heart insufficiency due to other causes; severe pulmonary, liver, and kidney dysfunction; severe anemia (Hb <100 g/L) and gastrointestinal disease; the existence of epilepsy history and/or treatment with antiepileptic drugs; and treatment with antidementia drugs and/or antipsychotics within the previous 2 weeks.

According to the Clinical Dementia Rating (CDR) Scale, the 125 patients with AD were classified into mild AD (n = 28), moderate AD (n = 42), and severe AD (n = 55) groups. Additionally, this study included an age-matched healthy control (HC) group (n = 40). The HC group comprised healthy volunteers who underwent comprehensive physical examinations and showed no history of neurological, psychiatric and/or endocrine diseases, disturbance of consciousness, or family history of dementia.

The protocol of this study was revised and approved by the ethics committees of the participating hospitals. All patients or their families provided informed written consent.

Assessment Measures

Evaluation of cognitive function using Mini-Mental State Examination. The Mini-Mental State Examination (MMSE) was administered by 2 experienced psychiatrists in a blinded manner. Mini-Mental State Examination is a 30-point questionnaire giving a total score ranging from 0 to 30. Items are generally classified according to the following 6 parameters: orientation of time and place; short-term memory; attention; computing capacity; language (including naming, retelling, comprehensive reading, and instructing); and visuospatial memory.[11] The cutoff values were normalized according to the level of education following the guidelines by Zhang.[12] Briefly, the illiterate group had a cutoff value of 17; the cutoff value of primary school education was 20; and the cutoff value of middle school education was 24.

Hachinski Ischemia Scale. Hachinski Ischemia Scale (HIS) was used for the differential diagnosis of dementia as described previously.[12] To ensure the credibility of patients and the repeatability of our results, HIS was administered by 2 professional psychiatrists in a blinded manner. The HIS maximum scale was 18 and patients with scores exceeding 7 were considered patients with vascular dementia. Alzheimer's disease diagnosis was considered if the HIS score was below 4.[12]

Evaluation of severity of dementia using CDR Scale. Clinical Dementia Rating is a 5-point scale used by clinicians to assess the severity of AD.[12] Clinical Dementia Rating was administered by 2 experienced psychiatrists in a blinded manner. In this study, the HC group scored 0 on the CDR scale, while scores of 1, 2, and 3 were defined as the mild, moderate, and severe AD groups, respectively. Items in the CDR scale are generally classified according to the following 7 parameters: memory, orientation, judgment, the ability to resolve problems, social affairs, family, and interest as well as self-care ability.[12]

Blood Collection and Laboratory Investigations

The collection of blood samples was approved by all enrolled patients and/or their family members. For each participant, a total of 5 mL venous blood was obtained following 6-hour fasting and left until complete coagulation. Next, samples were centrifuged for 10 minutes at 3500 r/min, and the serum was used directly for subsequent assays. Serum CER and CRP levels were analyzed by enzyme-linked immunosorbent assay (ELISA; Beckman Coulter, Brea, California) using commercially available kits (Beckman Coulter) according to the manufacturer's protocol. Uric acid and Hcy levels were analyzed by enzyme-linked colorimetry assay (Beckman Coulter) following the manufacturer's protocol. Serum copper, iron, and zinc were determined by photoelectric colorimetric assay (Wako Pure Chemical Industries, Ltd, Osaka, Japan) following the standard protocol.[13]

Statistical Analyses

Statistical analyses were performed using SPSS version 13.0 statistical software (IBM SPSS, Chicago, Illinois). All data were normally distributed. The observed indices were expressed as mean (standard deviation). The sex distribution in the groups was analyzed using a χ^2 test, and the pairwise comparison for the means in 2 groups was evaluated using the Student-Newman-Keuls (SNK-q) test. In this study, we observed that the SNK-q test was more appropriate when comparing the enrolled 4 groups together. We defined $\alpha = .05$ as the test criterion. A P value <.05 was considered statistically significant, while $P < .01$ indicated high statistical significance.

Results

Patients' Demographic and Clinical Characteristics

This study included 125 patients with AD classified into mild (n = 28), moderate (n = 42), and severe (n = 55) patients with AD groups with CDR scores of 1, 2, and 3, respectively. The

Table 1. Demographic Features for Healthy Control and Patients With Alzheimer Disease.

Groups	Total Number	M/F	I/P/M	Average Age (Years)	MMSE Score	HF/NF
Healthy control	40	21/19	16/20/4	74.17 (6.54)	24.17 (3.35)	0/40
Mild dementia	28	15/13	10/15/3	73.36 (5.98)	19.83 (3.27)	1/27
Moderate dementia	42	23/19	15/23/4	75.78 (6.74)	13.54 (2.98)	3/39
Severe dementia	55	30/25	20/29/6	77.83 (6.47)	5.62 (1.14)	4/51

Abbreviations: AD, Alzheimer's disease; HF/NF, have family history of heredity AD/no family history of heredity AD; I/P/M, illiterate/primary school/middle school; M/F, male/female; MMSE, Mini-Mental State Examination.

average age in the AD group was 73.36 (5.98), 75.78 (6.74), and 77.83 (6.47) years in the mild, moderate, and severe groups, respectively. In addition, 21 males and 19 females with an average age of 74.17 (6.54) were enrolled in the HC group. The HIS scores of all patients with AD and HC volunteers were less than 4. There was no statistically significant difference between the HC and the AD groups in terms of age, sex distribution, and level of education ($P > .05$). The patients' demographic characteristics are presented in Table 1.

Serum CER Levels in Patients With AD

The mean serum CER level in the HC group was 0.24 (0.54) g/L, whereas the average CER levels in the mild, moderate, and severe AD groups were 0.22 (0.52), 0.17 (0.48), and 0.15 (0.41) g/L, respectively. Comparison of these values using the SNK-q test indicated significant differences between the HC group and the moderate AD group ($q = 3.40$, $P = .049$), the HC and severe AD groups ($q = 3.74$, $P = .039$), the mild and moderate AD groups ($q = 3.35$, $P = .050$), and the mild and severe AD groups ($q = 3.40$, $P = .049$; Table 2).

Serum UA Levels in Patients With AD

The mean serum UA level in the HC group was 351.43 (54.68) μmol/L, whereas the average levels in the mild, moderate, and severe AD groups were 332.67 (52.19), 268.25 (48.74), and 225.71 (41.84) μmol/L, respectively. We observed significant differences in the UA levels between the HC group and the moderate AD group ($q = 3.46$, $P = .045$), the HC and severe AD groups ($q = 4.15$, $P = .014$), the mild AD and moderate AD groups ($q = 3.50$, $P = .044$), and the mild and the severe AD groups ($q = 3.99$, $P = .025$; Table 3).

Serum CRP Levels in Patients With AD

The average serum CRP level in the HC group was 6.14 (1.85) mg/L, whereas the average levels in the mild, moderate, and severe AD groups were 5.48 (1.61), 6.35 (1.24), and 19.84 (2.53) mg/L, respectively. We observed statistically significant differences between the HC group and the severe AD group ($q = 4.11$, $P = 0.015$), the mild and severe AD groups ($q = 4.23$, $P = .011$), and the moderate and severe AD groups ($q = 4.09$, $P = .015$; Table 4).

Table 2. Pairwise Comparison of Serum CER Levels Between Healthy Individuals and Patients With Alzheimer's Disease of Varying Severity.[a]

Groups	Mean Difference (g/L)	q	P Value
1, 2	0.02	0.51	.684
1, 3	0.07	3.40	.049
1, 4	0.09	3.74	.039
2, 3	0.05	3.35	.050
2, 4	0.07	3.40	.049
3, 4	0.02	0.51	.684

Abbreviations: AD, Alzheimer's disease; CER, ceruloplasmin; HC, healthy control.
[a]Group 1 represents HC group, group 2 is mild AD group, group 3 is moderate AD group, and group 4 is severe AD group. The pairwise comparison was performed for all permutations of the groups.

Table 3. Pairwise Comparison of Serum UA Levels Between Healthy Individuals and Patients With Alzheimer's Disease of Varying Severity.[a]

Groups	Mean Difference (μmol/L)	q	P Value
1, 2	18.76	0.61	.667
1, 3	83.18	3.45	.045
1, 4	125.72	4.15	.014
2, 3	64.42	3.50	.044
2, 4	106.96	3.99	.025
3, 4	42.54	1.74	.390

Abbreviations: AD, Alzheimer's disease; HC, healthy control; UA, uric acid.
[a]Group 1 represents HC group, group 2 is mild AD group, group 3 is moderate AD group, and group 4 is severe AD group. The pairwise comparison was performed for all permutations of the groups.

Table 4. Pairwise Comparison of Serum CRP Levels Between Healthy Individuals and Patients With Alzheimer's Disease of Varying Severity.[a]

Groups	Mean Difference (mg/L)	q	P Value
1, 2	0.66	1.78	.391
1, 3	−0.21	1.23	.429
1, 4	−13.70	4.11	.015
2, 3	−0.87	2.42	.107
2, 4	−14.36	4.23	.011
3, 4	−13.49	4.09	.015

Abbreviations: AD, Alzheimer's disease; CRP, C-reactive protein; HC, healthy control.
[a]Group 1 represents HC group, group 2 is mild AD group, group 3 is moderate AD group, and group 4 is severe AD group. The pairwise comparison was performed for all permutations of the groups.

Table 5. Pairwise Comparison of Serum Hcy Levels Between Healthy Individuals and Patients With Alzheimer Disease of Varying Severity.[a]

Groups	Mean Difference (μmol/L)	*q*	*P* Value
1, 2	2.17	1.81	.392
1, 3	1.29	1.13	.526
1, 4	−5.20	4.08	.015
2, 3	−0.88	0.92	.813
2, 4	−7.37	4.30	.009
3, 4	−6.49	4.10	.015

Abbreviations: AD, Alzheimer's disease; HC, healthy control; Hcy, homocysteine.
[a]Group 1 represents HC group, group 2 is mild AD group, group 3 is moderate AD group, and group 4 is severe AD group. The pairwise comparison was performed for all permutations of the groups.

Table 6. Pairwise Comparison of Serum Copper Levels Between Healthy Individuals and Patients With Alzheimer's Disease of Varying Severity.[a]

Groups	Mean Difference (μmol/L)	*q*	*P* Value
1, 2	−0.58	0.69	.788
1, 3	−3.99	3.63	.037
1, 4	−4.97	4.15	.014
2, 3	−3.41	3.34	.050
2, 4	−4.39	4.01	.025
3, 4	−0.98	2.48	.199

Abbreviations: AD, Alzheimer's disease; HC, healthy control.
[a]Group 1 represents HC group, group 2 is mild AD group, group 3 is moderate AD group, and group 4 is severe AD group. The pairwise comparison was performed for all permutations of the groups.

Serum Hcy Levels in Patients With AD

The average serum Hcy level in the HC group was 23.64 (7.58) mg/L, whereas the average levels in the mild, moderate, and severe AD groups were 21.47 (7.61), 22.35 (8.24), and 28.84 (8.53) mg/L, respectively. We observed statistically significant differences between the HC group and the severe AD group ($q = 4.08$, $P = .015$), the mild and severe AD groups ($q = 4.30$, $P = .009$), and the moderate and severe AD groups ($q = 4.10$, $P = .015$; Table 5).

Serum Copper Levels in Patients With AD

The average serum copper level in the HC group was 16.32 (6.54) μmol/L, whereas the serum copper levels in the mild, moderate, and severe AD groups were 16.90 (6.37), 20.31 (6.74), and 21.29 (6.92) μmol/L, respectively. Comparison of these average values using the SNK-*q* test indicated significant differences between the HC and the moderate AD groups ($q = 3.63$, $P = .037$), the HC group and the severe AD group ($q = 4.15$, $P = .014$), the mild and moderate AD groups ($q = 3.34$, $P = .050$), and the mild group and the severe AD group ($q = 4.01$, $P = .025$; Table 6).

Serum Iron Levels in Patients With AD

The average serum iron level in the HC group was 9.19 (4.71) μmol/L, whereas the average levels in the mild, moderate, and severe AD groups were 7.82 (4.67), 7.71 (4.42), and 7.28 (4.19) μmol/L, respectively. By comparing the average serum iron levels among the different groups, we observed significant differences between the HC group and the mild AD group ($q = 3.58$, $P = .041$), the HC group and the moderate AD group ($q = 3.88$, $P = .034$), and the HC group and the severe AD group ($q = 3.93$, $P = .027$; Table 7).

Serum Zinc Levels in Patients With AD

The average serum zinc level in the HC group was 100.67 (9.78) μmol/L, whereas the average levels in the mild, moderate, and severe AD groups were 86.78 (9.91), 66.48 (9.37), and 71.55 (8.97) μmol/L, respectively. Comparing the average values using the SNK-*q* test indicated significant differences between the HC group and the mild AD group ($q = 3.41$, $P = .049$), the HC group and the moderate AD group ($q = 4.17$, $P = .011$), the HC group and the severe AD group ($q = 4.11$, $P = .020$), the mild and moderate AD groups ($q = 3.54$, $P = .039$; and the mild and severe AD groups ($q = 3.44$, $P = .048$; Table 8).

Table 7. Pairwise Comparison of Serum Iron Levels Between Healthy Individuals and Patients With Alzheimer's Disease of Varying Severity Degrees.[a]

Groups	Mean Difference (μmol/L)	*q*	*P* Value
1, 2	1.37	3.58	.041
1, 3	1.48	3.88	.034
1, 4	1.91	3.93	.027
2, 3	0.11	0.65	.788
2, 4	0.54	0.98	.679
3, 4	0.43	1.25	.463

Abbreviations: AD, Alzheimer's disease; HC, healthy control.
[a]Group 1 represents HC group, group 2 is mild AD group, group 3 is moderate AD group, and group 4 is severe AD group. The pairwise comparison was performed for all permutations of the groups.

Table 8. Pairwise Comparison of Serum Zinc Levels Between Healthy Individuals and Patients With Alzheimer's Disease of Varying Severity Degrees.[a]

Groups	Mean Difference	*q*	*P* Value
1, 2	18.89	3.41	.049
1, 3	33.95	4.17	.011
1, 4	29.12	4.11	.020
2, 3	15.30	3.54	.039
2, 4	10.23	3.44	.048
3, 4	−5.07	1.58	.557

Abbreviations: AD, Alzheimer's disease; HC, healthy control.
[a]Group 1 represents HC group, group 2 is mild AD group, group 3 is moderate AD group, and group 4 is severe AD group. The pairwise comparison was performed for all permutations of the groups.

Table 9. Correlation Between MMSE Scores and Serum CER, UA, CRP, Copper, Iron, and Zinc Levels.[a]

Variables	*r*	*P* Value
Serum CER	0.473	.014
Serum UA	0.413	.034
Serum CRP	−0.226	.124
Serum Hcy	−0.223	.128
Serum copper	−0.526	.006
Serum iron	0.176	.108
Serum zinc	0.337	.009

Abbreviations: CER, ceruloplasmin; CRP, C-reactive protein; Hcy, homocysteine; MMSE, Mini-Mental State Examination; UA, uric acid.
[a]*r* is a partial correlation coefficient, which stands for the correlation between parameters and MMSE scores.

Table 10. Ordinal Logistic Regression Between Severity of AD and Serum CER, UA, CRP, Copper, Iron, and Zinc Levels.

Variables	*P*	OR	95% CI
Serum CER level (g/L)	.021	0.325	0.156-0.604
Serum UA level (mg/L)	.066	0.402	0.226-0.835
Serum CRP level (mg/L)	.173	18.116	12.367-25.447
Serum Hcy level (μmol/L)	.181	15.376	10.821-21.583
Serum copper level (μmol/L)	.016	10.255	7.389-20.073
Serum iron level (μmol/L)	.243	0.430	0.235-1.150
Serum zinc level (μmol/L)	.033	0.158	0.076-0.448

Abbreviations: AD, Alzheimer's disease; CER, ceruloplasmin; CI, confidence interval; CRP, C-reactive protein; Hcy, homocysteine; OR, odds ratio; UA, uric acid.

Correlation Between MMSE Scores and Serum CER, UA, CRP, Hcy, Copper, Iron, and Zinc Levels

Multiple linear relationships between the MMSE scores and serum CER, UA, CRP, Hcy, copper, iron, and zinc levels were calculated. A positive correlation was identified between the MMSE scores and serum CER, UA, and zinc levels ($P = .014$, .034, and .009, respectively), and a negative correlation was identified between the MMSE scores and serum copper levels ($P = .006$). On the other hand, there was no correlation between MMSE scores and serum CRP, Hcy, and iron levels ($P = .124$ and .109, respectively; Table 9).

Logistic Regression Between Severity of Dementia and Serum CER, UA, CRP, Hcy, Copper, Iron, and Zinc Levels

Furthermore, we carried out logistic regression analysis to identify independent factors associated with the severity of dementia. This analysis identified serum CER and zinc as independent protective factors associated with severity of AD, whereas the serum copper level was identified as a risk factor (Table 10). There was no significant association between the severity of dementia and serum UA, CRP, Hcy, and iron levels.

Discussion

Amyloid plaques and neurofibrillary tangles are histopathological hallmarks of AD.[1] Amyloid β (Aβ) is a primary component of neural inflammatory plaques found in brain regions that control learning and memory.[14] The level of Aβ protein is tightly controlled by the rate of its production from the Aβ protein precursor and the rate of its degradation via the Aβ-degrading proteases. Increased Aβ production or decreased clearance was demonstrated to be crucial in AD pathogenesis.[15] The methionine-35 of $A\beta_{42}$ would generate much more reactive oxygen and not play a key role in plaque deposits.[16] Furthermore, OS and functional abnormalities in the mitochondrial function were also implicated with the development of AD.[17]Serum CER, UA, CRP, and Hcy are well-documented OS markers.[6,18,19] Furthermore, levels of metal ions including copper, iron, and zinc can predict the progression of OS.[20] Therefore, in this study, we investigated the relationships between AD severity and serum levels of CER, UA, CRP, and Hcy, as well as AD severity and several metal ions.

Here, we observed a correlation between the severity of AD (demonstrated by the degeneration of cognitive function) and the decreased levels of serum CER. Furthermore, linear regression analysis demonstrated a positive correlation between serum CER levels and MMSE scores. Previous studies proved that low levels of CER promoted the entry and accumulation of free Fe^{2+} into the CNS resulting in the induction of OS-mediated injury, known as Felton reaction.[21,22] Hydroxyl radicals and other reactive oxygen species produced in the Felton reaction attack macromolecules, including DNA and proteins, and start lipid peroxide reaction. Several studies previously demonstrated that decreased CER levels are usually accompanied by increased levels of serum non–CER-bound copper. Free copper will interact with the amyloid precursor protein and Aβ leading to the generation of more hydroxyl radicals.[23] Furthermore, it was previously shown that the combination of Aβ and copper results in the formation of neurotoxic Aβ: copper complexes. These complexes can oxidize cholesterol generating 7-hydroxycholesterol which may intervene with the role of low-density lipoprotein receptor-related protein 1 in suppressing the clearance of Aβ protein.[24] The abovementioned observations imply that decreased CER levels can indeed affect the severity of AD.

Our present study indicated a positive correlation between serum UA levels and MMSE scores. Uric acid has a critical role in relieving OS through removing free radicals and chelating metal ions.[25] Euser et al previously demonstrated that hyperuricemia was associated with decreased risk of dementia.[26] Moreover, Schretlen et al observed that elevated UA levels can lead to impaired cognitive function.[27] In this study, results indicated a positive correlation between the serum zinc levels and MMSE scores. Previous studies suggested that zinc ions could activate matrix metalloproteinase, insulin-degrading enzyme, and enkephalinase possibly leading to the degradation of Aβ.[28] Furthermore, a negative correlation between zinc levels and Aβ in cerebrospinal fluid of HC participants was previously established.[29]

Alterations in the serum levels of CER, UA, CRP, Hcy, copper, iron, and zinc were clearly observed in patients with AD, and a significant correlation was identified between the severity of dementia and serum CER, UA, copper, and zinc levels, especially in patients with moderate or severe AD. Therefore, decreased levels of serum CER, UA, and zinc as well as increased levels of serum copper can be possible risk factors that determine the severity of AD. Nevertheless, this study had few limitations, including a small sample size and lack of cerebrospinal fluid markers or neuroimaging results, which can affect the interpretation accuracy. Furthermore, we did not examine the effects of other traumatic head injuries and other genetic factors. Additionally, we could not perform the genetic testing to analyze possible mutations due to technical limitations. In this study, we did not directly examine the correlation between the stage of cognitive dysfunction and the levels of free radicals, though we believe that OS markers and metal ions affect patients with AD cognition by altering the levels of free radicals. In future studies, we will analyze the mutation and overproliferation of DNA and examine the levels of free radicals in patients with AD. It is worth mentioning that we excluded patients treated for hypertension to ensure consistency and comparability of the patients. Recent reports have indicated that β-blockers and angiotensin-converting enzyme inhibitors were beneficial in improving the cognitive function of patients with AD.[30,31]

To date, there are no effective treatments to cure AD or prevent its development. Nevertheless, results obtained from the current study can be instrumental for developing new approaches for AD treatment. Based on the close correlation between OS and AD, our findings support the theory that antioxidant treatment for OS may be an important strategy AD treatment.[32] Previous research indicated that the antioxidant agent (latrepirdine) could suppress neurodegenerative diseases and metal ion chelating agents could relieve AD symptoms and delay its progression.[33-35]

Declaration of Conflicting Interests

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

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