Diagnostic Brain Medicine

ORIGINAL RESEARCH

Open Access

Correlation Analysis of Cognitive Impairment with Oxidative Stress and Inflammatory Indicators in Elderly Patients with Alzheimer's Disease

Wujie Zhai[1, #, *] and Wenjie Zhai[2, #]

[1]Sinochem Second Construction Group Hospital,030000 Taiyuan, Shanxi, China

[2]Xi County Longquan Town Health Centre, 245000 Huangshan, Anhui, China

Keywords

Elder, Alzheimer's disease, Cognitive function, Oxidative stress, Inflammatory indicators

***Correspondence**

Wujie Zhai, Sinochem Erjian Group Hospital, No.26 Yijing Street, Jinyuan District, Taiyuan City, Shanxi Province.

E-mail: zhaiwujie7322759@163.com

[#]These authors contributed equally.

Received: 14 February 2023; Revised: 28 February 2023; Accepted: 6 March 2023; Published: 23 June 2023

Diagnostic Brain Medicine 2023; 4(2): 39-44

Abstract

Objective To analyze the correlation between cognitive impairment with oxidative stress and inflammatory indicators in elderly patients with alzheimer's disease (AD). **Methods** A total of 45 elderly patients with AD who were admitted to our hospital from May 2018 to September 2020 were recruited to the AD disease group, and another 45 healthy subjects were recruited to the healthy control group during the same period. The Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog), levels of serum oxidative stress [malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px)] and inflammatory indexes [tumor necrosis factor (TNF)-α, interleukin (IL)-8, IL-6] of all the subjects were determined. The Pearson correlation analysis was used to analyze the correlation between cognitive function with oxidative stress and inflammatory indicators in AD group. **Results** The ADAS-cog score of AD disease group was significantly higher than that of healthy control group (P<0.05); the level of MDA in AD disease group was greatly higher than that in healthy control group (P<0.05), and the levels of SOD and GSH-Px in AD disease group were sharply lower than that in healthy control group (P<0.05). The levels of TNF-α, IL-8 and IL-6 in AD disease group were significantly higher than those in healthy control group (P<0.05). The ADAS-cog score of AD disease group was positively correlated with the levels of serum TNF-α, IL-8, IL-6 and MDA (r=0.407, 0.342, 0.433, 0.440; P<0.05), and was negatively correlated with the levels of SOD and GSH-Px (r=-0.486, -0.434; P<0.05). **Conclusion** The cognitive function of elderly patients with AD was sharply reduced, and there were relatively serious oxidative stress and inflammatory reactions in the body. In addition, the cognitive function of patients was closely correlated with the oxidative stress and inflammatory indicators.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that occurs in the elderly. It is insidious in its onset and progressive in its development, and is characterized clinically by memory loss, aphasia, personality changes, cognitive impairment and other manifestations of dementia, which seriously affects the quality of life of patients and their families [1]. Currently, it is known that family genetics, head trauma, environment and estrogen may be related to the development of the disease [2], but its exact pathogenesis has not been elucidated, and there is still a lack of effective preventive means and interventions in clinical practice. With further research on AD, it has been suggested that oxidative stress and inflammatory damage are closely related to the development of the disease [3,4], but the specific role of it in the disease process is still unclear. Therefore, in this study, we measured the levels of oxidative stress and inflammatory indicators in elderly AD patients, and further analyzed the correlation between the changes in their levels and the severity of cognitive function of patients, in order to investigate the pathogenesis of the disease in depth and provide directional reference for the subsequent treatment of patients.

Data and methods

Clinical data

General data

Forty-five elderly AD patients attending our hospital between May 2018 and September 2020 were selected as the AD disease group, and another 45 healthy people with physical examination at the same period were selected as the healthy control group. The study was approved by the Medical Ethics Committee of our hospital, and all the subjects and their families were informed of the specific contents of the study and signed the informed consent form. There was no significant difference between the two groups in terms of gender, age, body mass index (BMI), duration of illness, history of hypertension, history of smoking and history of alcohol consumption (P>0.05), which were comparable, see Table 1.

Table 1 Comparison of general information between the two groups

Groups	Cases	Gender (male/female)	Age (years old)	BMI (kg/m^2)	Disease course (year)	Hypertension [case(%)]	Smoking [case(%)]	Drinking [case(%)]
AD group	45	25/20	67.95±2.76	21.59±1.45	2.26±1.25	23(51.11)	33(73.33)	27(60.00)
Control group	45	22/23	69.01±2.82	22.10±1.50	-	20(46.66)	29(64.44)	29(64.44)
t/χ^2		0.401	-1.082	-1.640	-	0.320	1.877	0.340
P		0.527	0.075	0.105	-	0.572	0.171	0.560

Inclusion and exclusion criteria

Inclusion criteria: all the patients in the AD disease group were clinically diagnosed with AD [5], aged >65 years, and all met the diagnostic criteria for AD in the American Diagnostic and Statistical Manual of Mental Disorders. Exclusion criteria: patients with severe metabolic diseases, malignant tumors and other cranio-cerebral pathologies; patients with combined dysfunction of vital organs such as heart, liver, kidney and blood system; patients with other diseases that may affect cognitive function; patients who were unable to cooperate to complete the study.

Evaluation of cognitive function

The ADAS-cog was used to evaluate the cognitive function of all the subjects [6], including orientation, language, structure, use of ideas, immediate word recall and word recognition, etc.. A total of 12 questions were used, with a total assessment time of about 15-30 minutes and a total score of 0-75 points. Higher scores indicate more severe cognitive impairment.

Observation indexes

We collected 5 ml of blood from all the subjects with an empty stomach in the early morning, and the serum was centrifuged and used to measure the levels of oxidative stress and inflammatory indexes: 1) oxidative stress indexes: serum malondialdehyde (MDA) level was measured by the thiobarbituric acid colourimetric method; serum superoxide dismutase (SOD) level was measured by the xanthine oxidase colourimetric method; serum glutathione level was measured by the dithiodinitrobenzoic acid colourimetric method. (2) Inflammatory indexes: serum tumour necrosis factor (TNF)-α, interleukin (IL)-8 and IL-6 levels were measured by enzyme-linked immunosorbent assay (Nanjing Jiancheng Institute of Biological Engineering).

Statistical methods

Statistical analysis was performed using SPSS 20.0. Count data were compared using the χ2 test, measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$) and compared using the t-test. Correlations were analyzed using Pearson correlation analysis, and differences were considered statistically significant at P<0.05.

Results

Comparison of ADAS-cog scores between the two groups

The ADAS-cog score was (25.68±4.15) in the AD group and (6.51±3.10) in the control group. The ADAS-cog score was significantly higher in the AD group than in the control group (p<0.05).

Comparison of oxidative stress index levels between the two groups

The MDA levels in the AD disease group were significantly higher than those in the healthy control group (P<0.05), and the SOD and GSH-Px levels in the AD group were significantly lower than those in the control group (P<0.05), see Table 2.

Table 2 Comparison of oxidative stress index levels between the two groups

Groups	Cases	MDA (μmol/L)	SOD (U/mL)	GSH-Px (U)
AD group	45	6.95±1.35	60.59±4.25	150.28±31.56
Control group	45	4.89±1.26	70.24±5.65	198.25±35.66
t		7.483	-9.156	-6.758
P		0.000	0.000	0.000

Comparison of inflammatory index levels between the two groups

The levels of TNF-α, IL-8 and IL-6 were significantly higher in the AD group than in the healthy control group (p<0.05), see Table 3.

Table 3 Comparison of inflammatory index levels between the two groups

Groups	Cases	TNF-α (ng/L)	IL-8 (ng/L)	IL-6 (pg/mL)
AD group	45	23.15±5.26	19.35±4.52	128.15±25.25
Control group	45	16.05±5.45	12.89±4.19	109.28±24.32
t		6.288	7.031	3.611
P		0.000	0.000	0.001

Correlation between ADAS-cog scores and levels of inflammatory and oxidative stress indicators in the AD group

ADAS-cog scores in the AD group were positively correlated with serum TNF-α, IL-8, IL-6 and MDA levels (r=0.407, 0.342, 0.433, 0.440; P<0.05) and negatively correlated with SOD and GSH-Px levels (r=-0.486, -0.434; P<0.05), see Figure 1.

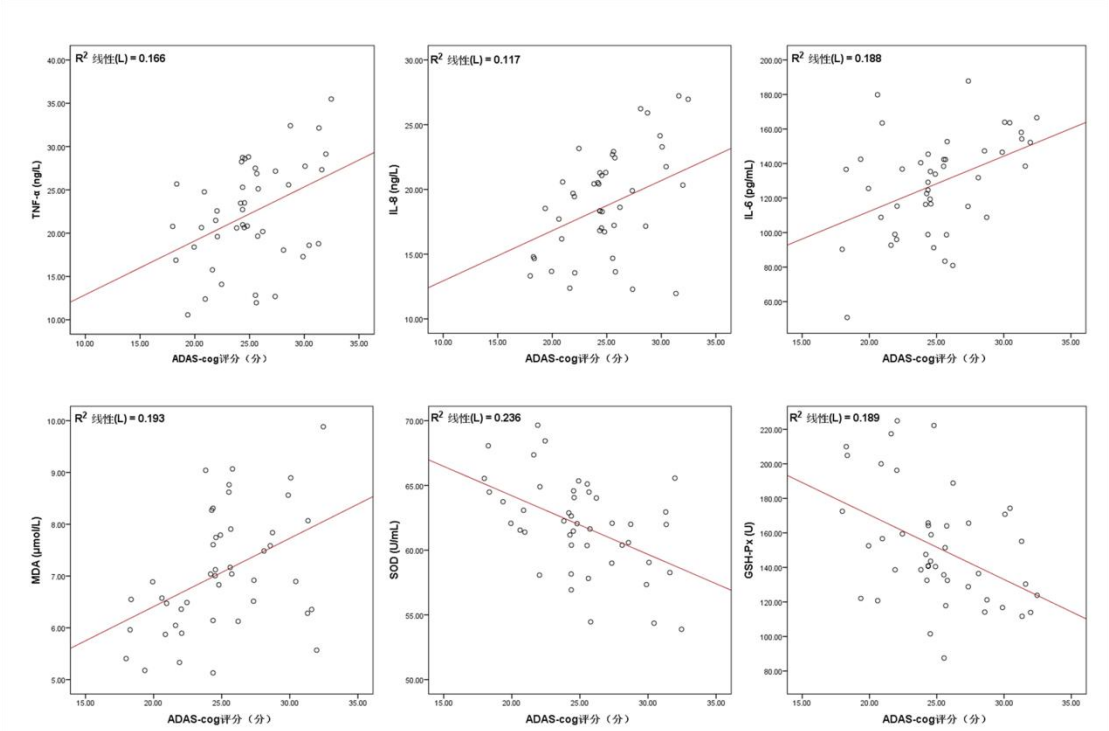

Figure 1 Correlation of ADAS-cog scores with levels of inflammatory and oxidative stress indicators in the AD group

Discussion

AD is a common disease among the elderly, and with the increasing problem of ageing in China, the incidence of AD is gradually increasing, and its overall prevalence among people over 65 years of age is about 2-7% [7,8]. In clinical manifestations, we found that AD patients with AD have significantly higher ADAS-cog scores than healthy individuals, which is consistent with the results of previous studies [9], indicating the existence of certain cognitive dysfunction in AD patients. It has been suggested [10] that when elderly people fall ill, pathological changes such as β-like amyloid (Aβ) deposition, neurofibrillary tangles, inhibition of neurotransmitter transmission and mitochondrial damage will occur in brain tissues, which in turn leads to local lesions in the temporal lobe, parietal lobe and hippocampus, as well as whole brain atrophy, ultimately triggering cognitive dysfunction. Butterfield DA et al. pointed out [11,12] that AD patients not only have these pathological symptoms in the brain, but also have altered redox status, in which oxidative stress manifestations such as glycosylation products, oxidized proteins, lipid peroxidation reaction end products and oxidative modification of nucleic acids are predominant. In addition, according to Newcombe EA et al [13], the inflammatory response is a complex cellular molecular defence mechanism whose mediator levels are significantly up-regulated in the brains of AD patients, not only acting as a pathogenic factor, highly activating microglia and activating astrocytes, but also acting as a feedback factor causing high levels of interleukin expression. All these studies suggest that oxidative stress and inflammatory responses may play a role in the development of AD and disease progression.

Oxidative stress is a pathological state in which there is an imbalance between oxidative and antioxidant functions in the body, with a potential of oxidative effects. Clinically, MDA, SOD and GSH-Px are often used to reflect the oxidative stress state of the body, of which MDA is the end product of lipid peroxidation and oxygen free radicals that are cytotoxic and can damage cell membranes. SOD and GSH-Px are

antioxidant enzymes, SOD, a key antioxidant enzyme, has the effect of scavenging free radicals, thus reducing the cellular damage of oxygen free radicals and promoting cellular repair; GSH-Px is a peroxidolytic enzyme, and its active component is selenocysteine, which can reduce toxic peroxides to further prevent the cell membrane from being attacked [15]. A previous study [16] showed that with the decrease of MDA level and the increase of SOD level, the disease progression of AD patients could be effectively delayed, which is similar to the results of this study. We found that the MDA levels of elderly AD patients were significantly higher than those of healthy individuals and negatively correlated with cognitive function, while SOD and GSH-Px levels were significantly lower and positively correlated with cognitive function, indicating that the level of oxidative stress in the organism of AD patients was higher and closely correlated with the degree of impairment of cognitive function, which may be due to oxidative stress dysfunction in AD patients and the accumulation of hydrides in the brain. Such a result might be explained by a disruption of oxidative stress in AD patients, resulting in neurological damage, which leads to neurofibrillary tangles and cognitive impairment.

Research on the pathogenesis of AD showed [17] that inflammatory factors are involved in the pathological damage of AD in early-onset dementia, represented by TNF-α, IL-8 and IL-6. The above inflammatory indicators are all important pro-inflammatory factors, of which IL-8 is a polygenic inflammatory factor that can chemotactic neutrophils, T lymphocytes and basophils, aggregating inflammatory cells; TNF-α promotes the survival of astrocytes and increases the synthesis of neurological substances such as nitric oxide and glutamate, thus exerting a neurotoxic effect; IL-6 is synthesised and secreted by glial cells and has an apoptosis-inducing effect on neurons, as well as activating acute proteins. It can be seen that the combined effect of multiple inflammatory factors can induce the development of AD. In this study, we found that the levels of inflammatory indicators such as TNF-α, IL-8 and IL-6 were significantly higher in AD patients than in healthy controls, and were positively correlated with cognitive function, suggesting that the inflammatory response may be the pathogenesis of cognitive dysfunction in AD patients. In a related study, Cattaneo A et al found [18] that cognitive impairment in AD patients may be related to dysregulation of anti-inflammatory factors in the organism. In animal studies, Shojaie M et al [19] suggested that regulating IL-6 and TNF-α levels improved the cognitive function of mice and protected mouse brain tissue cells. In short, the inflammatory response has an important role in cognitive function. Overexpression of TNF-α, IL-8 and IL-6 inhibits hippocampal progenitor cells in the brain of AD patients, activates astrocytes as well as microglia in the brain, increases glutamate excitotoxicity, and triggers neuroinflammation, which ultimately induces cognitive dysfunction [20].

In summary, impaired cognitive function of elderly AD patients show more serious oxidative stress and inflammatory response in the body, and the cognitive function of patients is closely correlated with oxidative stress and inflammatory indicators.

Acknowledgements

Not applicable.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization, Data curation and Writing-Original draft, Wen.J.Z; Writing-review and editing, Wu.J.Z; All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee, and the patients were informed and consented.

Funding

This research received no external funding.

Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary Material

Not applicable

References

[1] Mancino R, Martucci A, Cesareo M, et al. Glaucoma and Alzheimer Disease: A Single Age-Related Neurodegenerative Disease of the Brain [J]. Curr Neuropharmacol, 2017, 16(7): 971-977.

[2] Tiwari S, Atluri V, Kaushik A, et al. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics [J]. Int J Nanomedicine, 2019, 14:5541-5554.

[3] Heppner F L, Ransohoff R M, Becher B. Immune attack: the role of inflammation in Alzheimer disease [J]. Nat Rev Neurosci, 2015, 16(6):358-372.

[4] Kamat PK, Kalani A, Rai S, et al. Mechanism of Oxidative Stress and Synapse Dysfunction in the Pathogenesis of Alzheimer's Disease: Understanding the Therapeutics Strategies [J]. Mol Neurobiol, 2016, 53(1):648-661.

[5] Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment [J]. F1000Res, 2018, 7:F1000 Faculty Rev-1161.

[6] Kueper JK, Speechley M, Montero-Odasso M. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): Modifications and Responsiveness in Pre-Dementia Populations. A Narrative Review [J]. J Alzheimers Dis, 2018, 63(2):423-444.

[7] Lane CA, Hardy J, Schott JM. Alzheimer's disease [J]. Eur J Neurol, 2018, 25(1):59-70.

[8] Bondi MW, Edmonds EC, Salmon DP. Alzheimer's Disease: Past, Present, and Future [J]. J Int Neuropsychol Soc, 2017, 23(9-10):818-831.

[9] Harrison JE, Rentz DM, Brashear HR, et al. Psychometric Evaluation of the Neuropsychological Test Battery in Individuals with Normal Cognition, Mild Cognitive Impairment, or Mild to Moderate Alzheimer's Disease: Results from a Longitudinal Study [J]. J Prev Alzheimers Dis, 2018, 5(4): 236-244.

[10] Reiss AB, Arain HA, Stecker MM, et al. Amyloid toxicity in Alzheimer's disease [J]. Rev Neurosci, 2018, 29(6):613-627.

[11] Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease [J]. Nat Rev Neurosci, 2019, 20(3):148-160.

[12] Umeno A, V Biju, Y Yoshida, In vivo ROS production and use of oxidative stress-derived biomarkers to detect the onset of diseases such as Alzheimer's disease, Parkinson's disease, and diabetes [J]. Free Radic Res, 2017. 51(4): 413-427.

[13] Newcombe EA, Camats-Perna J, Silva ML, et al. Inflammation: the link between comorbidities, genetics, and Alzheimer's disease [J]. J Neuroinflammation, 2018, 15(1):276.

[14] Lopez-Riquelme N, Alom-Poveda J, Viciano - Morote N, et al. Apolipoprotein E epsilon4 allele and malondialdehyde level are independent risk factors for Alzheimer's disease [J]. SAGE Open Med, 2016. 4: p. 2050312115626731.

[15] Islam MT. Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders [J]. Neurol Res, 2017, 39(1):73-82.

[16] Mancini S, Balducci C, Micotti E, et al. Multifunctional liposomes delay phenotype progression and prevent memory impairment in a presymptomatic stage mouse model of Alzheimer disease [J]. J Control Release, 2017(258): 121-129.

[17] Zhu Y, Chai YL, Hilal S, et al. Serum IL-8 is a marker of white-matter hyperintensities in patients with Alzheimer's disease [J]. Alzheimers Dement (Amst), 2017, 7:41-47.

[18] Cattaneo A, Cattane N, Galluzzi S, et al. INDIA-FBP Group. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly [J]. Neurobiol Aging, 2017, 49:60-68.

[19] Shojaie M, Ghanbari F, Shojaie N. Intermittent fasting could ameliorate cognitive function against distress by regulation of inflammatory response pathway [J]. J Adv Res, 2017, 8(6):697-701.

[20] Fakhoury M. Microglia and Astrocytes in Alzheimer's Disease: Implications for Therapy [J]. Curr Neuropharmacol. 2018, 16(5):508-518.