



Retrospective Cohort Study

Correlative factors of poor prognosis and abnormal cellular immune function in patients with Alzheimer's disease

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Abstract

BACKGROUND

Alzheimer's disease (AD) is a serious disease causing human dementia and social problems. The quality of life and prognosis of AD patients have attracted much attention. The role of chronic immune inflammation in the pathogenesis of AD is becoming more and more important.

AIM

To study the relationship among cognitive dysfunction, abnormal cellular immune function, neuroimaging results and poor prognostic factors in patients.

METHODS

A retrospective analysis of 62 hospitalized patients clinical diagnosed with AD who were admitted to our hospital from November 2015 to November 2020. Collect cognitive dysfunction performance characteristics, laboratory test data and neuroimaging data from medical records within 24 h of admission, including Mini Mental State Examination Scale score, drawing clock test, blood T lymphocyte subsets, and neutrophils and lymphocyte ratio (NLR), disturbance of consciousness, extrapyramidal symptoms, electroencephalogram (EEG) and head nucleus magnetic spectroscopy (MRS) and other data. Multivariate logistic regression analysis was used to determine independent prognostic factors. the modified Rankin scale (mRS) was used to determine whether the prognosis was good. The correlation between drug treatment and prognostic mRS score was tested by the rank sum test.

RESULTS

Univariate analysis showed that abnormal cellular immune function, extrapyramidal symptoms, obvious disturbance of consciousness, abnormal EEG, increased NLR, abnormal MRS, and complicated pneumonia were related to the poor prognosis of AD patients. Multivariate logistic regression analysis showed that the decrease in the proportion of T lymphocytes in the blood after abnormal cellular immune function (odd ratio: 2.078, 95% confidence interval: 1.156-3.986, $P < 0.05$) was an independent risk factor for predicting the poor prognosis of AD. The number of days of donepezil treatment to improve cognitive function was negatively correlated with mRS score ($r = 0.578$, $P < 0.05$).

CONCLUSION

The decrease in the proportion of T lymphocytes may have predictive value for the poor prognosis of AD. It is recommended that the proportion of T lymphocytes $< 55\%$ is used as the cut-off threshold for predicting the poor prognosis of AD. The early and continuous drug treatment is associated with a good prognosis.

Key Words: Alzheimer's disease; Cellular immunity; Prognosis; T lymphocytes; Magnetic resonance spectroscopy

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Core Tip: Abnormal cellular immune function, extrapyramidal symptoms, abnormal electroencephalogram, increased neutrophils and lymphocyte ratio, abnormal magnetic spectroscopy, and complicated pneumonia were related to the poor prognosis of Alzheimer's disease (AD) patients. The decrease in the proportion of T lymphocytes in the blood after abnormal cellular immune function was an independent risk factor for predicting the poor prognosis of AD. The number of days of donepezil treatment to improve cognitive function was negatively correlated with modified Rankin scale score. The decrease in the proportion of T lymphocytes may have predictive value for the poor prognosis of AD.

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease with severe cognitive dysfunction. The prominent clinical manifestations are memory loss, confusion of thinking and logic, and abnormal mental behavior. It accounts for about 40%-60% of dementia patients[1,2]. At present, it is also inclined to think that AD is a chronic inflammatory disease mediated by abnormal autoimmune function. Mononuclear RNA sequencing and transcriptomics analysis show that the abnormal changes in microglia in the brain of AD patients induce a series of abnormal immune function. The activation of abnormal inflammasome represented by nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor protein 3 (NLRP3) inflammasome mediates the secretion of many immune inflammatory factors and subsequent cascades of chronic cascades reactions in immune inflammation[3,4]. The amyloid β ($A\beta$) peptide produced by abnormal neurons precipitates and aggregates outside the cell. The hyperphosphorylation of tau protein can also easily cause aggregation, leading to neuron and nerve synaptic dysfunction and cell death, especially small glial cells. Reactive proliferation of glial cells often causes secondary cytopathological reactions in diseased brain regions[5]. The activation of NLRP3 inflammasome promotes the aggregation of $A\beta$ protein and the pathological formation of AD. The activation of NLRP3 inflammasome also contributes to the phosphorylation of tau protein and the accelerated development of AD. The interaction between $A\beta$ and tau protein promotes the progression of AD. The onset and development of AD are usually mediated by abnormal immune function[6-8].

At present, the diagnostic criteria of AD mostly depend on the screening of cognitive function scale and the exclusion of similar diseases. Although there are some biochemical markers of dementia in serum or cerebrospinal fluid (CSF), their specificity and sensitivity are not high[9,10]. Combining some biochemical markers in blood or CSF for early diagnosis of AD may be a direction of future efforts, among which some biochemical markers related to immunity have great research prospects. Some scholars have combined the detection results of magnetic resonance spectroscopy (MRS) with blood biochemical markers and achieved good results[11]. On the other hand, the research on the factors affecting the prognosis of AD also has important clinical and social significance. Some AD patients may have a long life, but whether this longevity has social value is worth exploring. Longevity with obvious lack of quality of life and heavy burden on families may not be worth advocating. We need to make AD patients live a healthy life and return to society as much as possible [12,13].

The role of chronic immune inflammation in the pathogenesis of AD is becoming more and more important. The ratio of neutrophil to lymphocyte (NLR) in blood is an important systemic inflammatory biomarker. NLR is calculated by absolute counting of neutrophils divided by absolute counts of lymphocytes. NLR has been reported to be increased in

diabetes, hypertension, myocardial infarction, stroke and some tumor patients, which may be a new index to evaluate the prognosis of these patients[14-16]. The detection of T lymphocytes, B lymphocytes and natural killer cells in blood by flow cytometry can evaluate whether the immune function of AD patients is abnormal[17]. Combined with the detection of relevant biochemical markers and electroencephalogram (EEG) wave indexes by cranial MRS, it has great clinical significance for the early diagnosis and prognosis evaluation of AD patients. As far as we know, little research work has been carried out in this regard[18-20]. Therefore, this study focuses on the correlation between abnormal immune function and adverse prognostic factors in AD patients, and hope to find some valuable clues.

MATERIALS AND METHODS

Case study

This retrospective case study was reviewed and approved by the Medical Ethics Committee of the Third Affiliated Hospital of Guizhou Medical University in China. AD patients and their families hospitalized in the Department of Neurology and Psychiatry of the Third Affiliated Hospital of Guizhou Medical University were told to participate in the study and signed an informed consent form in accordance with the Declaration of Helsinki. The researchers checked the electronic medical records of 229 patients initially diagnosed with various types of dementia. These cases were patients who were discharged from the hospital between November 2015 and November 2020. The researchers re-evaluated the basis for the diagnosis of dementia in these cases, first confirmed or ruled out dementia through the Mini Mental State Examination Scale (MMSE) and the Cognitive Function Screening Scale, and then based on the medical history, clinical manifestations, and laboratory test results. In the diagnosis of AD, pay special attention to the use of the Harkinski Ischemic Scale to identify AD. Excluded 14 patients with incomplete data and 7 patients lacking the basis for the diagnosis of dementia scales. The remaining 208 patients with various types of dementia were further differentiated, and 87 patients with vascular dementia (VD) and 53 patients with other non-AD dementia were excluded. AD is roughly equivalent to the dementia of phlegm obstruction in Chinese medicine. VD is roughly equivalent to the dementia of qi stagnation and blood stasis in Chinese Medicine.

The 68 patients in this retrospective study are all clinically diagnosed AD patients. The 68 AD patients who met the needs of this study were selected for follow-up. After the patients are discharged from the hospital, they will be followed up and followed up by family members or guardians by telephone every 3 months. The prognosis will be assessed after detailed inquiries, and semi-quantitative according to the classic scale.

Data collection

Collect the following medical history and clinical data: Age of onset, gender, chief complaint, duration of disease, first symptoms, other symptoms, main positive signs, cranial magnetic resonance imaging (MRI), cranial MRS, EEG, blood routine, blood immunity Results of cell examination and drug treatment. The main metabolites detected by MRS include N-acetylaspartate (NAA), creatine (Cr), choline (Cho), inositol (MI), *etc.* NAA/Cr ratio and MI/Cr ratio were collected as key analysis indicators. Regarding EEG data, it is mainly to pay attention to the abnormal β wave and slow wave (θ wave and δ wave), especially the ratio of $(\theta + \delta)$ to $(\alpha + \beta)$ in the whole brain $[(\theta + \delta)/(\alpha + \beta)]$. We also pay attention to the ratio of neutrophils to lymphocytes (NLR) in the blood. The percentage values of T lymphocytes, B lymphocytes, and natural killer (NK) cells detected by flow cytometry are also collected. As the value of A β protein and tau protein in the blood in the diagnosis of AD is controversial sometimes, this study was not collected. The decrease of A β 42 protein in the CSF and the increase of phosphorylated tau protein do have certain value in the diagnosis of AD, but there are many lacks of data in this group of cases, and they have not been collected. In addition, we collected MMSE score data and cognitive function screening scale scores for AD patients.

Prognosis assessment

The modified rankin scale (mRS) was used to assess neurological function at admission, discharge, and follow-up. There are 6 grades of mRS score: 0 score is for full recovery; a score of 1 score is defined as having no apparent dysfunction or being able to perform daily life and work tasks despite symptoms; 2 score is mild disability, but basically able to complete daily life and work tasks independently; 3 score is moderate disability, unable to complete all previous activities, difficult to handle own affairs independently; 4 score is severely disabled and needs to be cared for by someone else; 5 score is severe disability who require intensive care by medical staff; and 6 score is defined as death case.

According to the mRS during the follow-up period, all patients were divided into two groups: Those with mRS score of 0-2 scores were defined as "good prognosis"; 3-6 scores was defined as "poor prognosis".

Flow cytometry to detect cellular immune indicators

The FC500 automatic flow cytometer was used to perform the detection by direct immunofluorescence. The percentage of quantitative counts of T lymphocytes, B lymphocytes, and NK cells in the blood of patients was measured at one time. FITC-labeled anti-CD mAbs and normal mouse IgG were prepared. Cell wash with 2% BSA, 0.1% NaN and PBS. The fixative was prepared to a volume of 100 mL with 25% glutaraldehyde 3.2 mL, 2 g glucose, and BSA-free cell wash. Debug the flow cytometer. 10^6 PBMC were added to each experimental tube, centrifuged at 1500 r/min for 3 min, and the supernatant was discarded. Add 20 mL of fluorescein-labeled anti-CD mAb, mix well; incubate at 4 °C for 60 min, add cell wash, centrifuge at 1500 r/min for 3 min, wash repeatedly 3 times; use cell wash to restore volume to 0.5 mL, add fixative 20 mL, mix; carefully check on the machine.

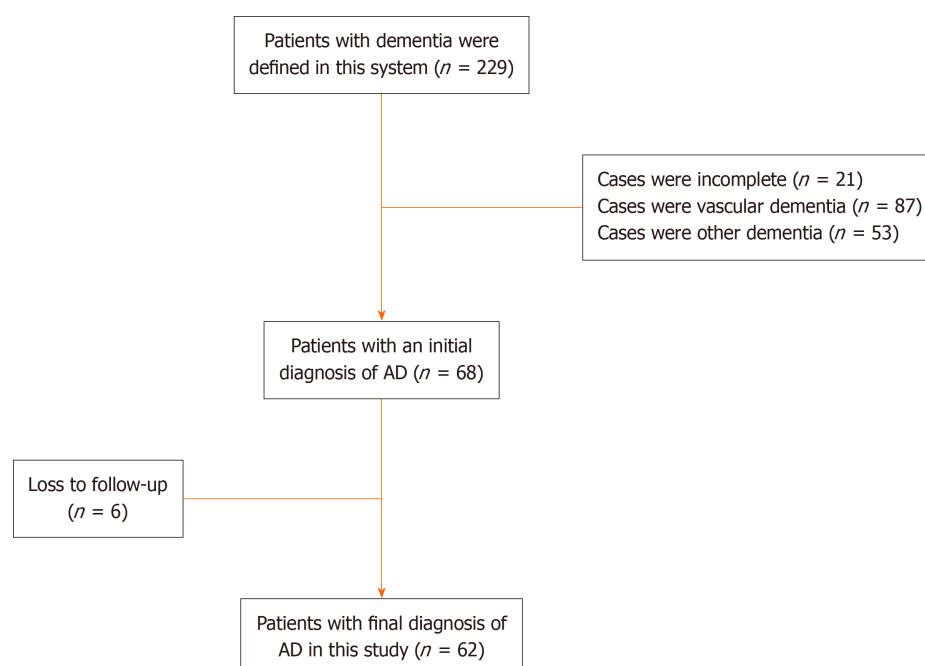


Figure 1 Flowchart of the study. AD: Alzheimer's disease.

Statistical analysis

SPSS software was used for statistical analysis (version 17.0). The data collected are expressed as mean \pm SD or median (range). Count data is expressed as a ratio or percentage. Univariate correlation analysis was used to compare the differences between the two groups. Student *t* test or Mann Whitney test is used for measurement data, *t* test is used for variables with normal distribution, and Mann Whitney test is used for variables with non normal distribution. The counting data were compared by chi square test. Logistic regression analysis was used to determine the independent risk factors of poor prognosis. Differences in mRS scores between two groups were determined using Spearman rank correlation test. The best cut-off value of NAA/Cr as a prognostic index of AD was determined by the analysis of receptor working curve (ROC). *P* values less than 0.05 (bilateral) were considered statistically significant.

RESULTS

Basic information of clinical data

Through the electronic medical records database of the inpatient department and medical record room of the hospital, 229 cases of patients with clinical diagnosis of single or combined dementia were collected, including 87 cases of VD, 68 cases of AD, and 53 cases of other dementia. These patients with other types of dementia included 3 cases of frontotemporal dementia, 2 cases of Lewy body dementia, 5 cases of Parkinson's disease dementia, 10 cases of chronic alcoholism dementia, 3 cases of dementia after carbon monoxide poisoning, 2 cases of dementia after AIDS infection, 3 cases of hypothyroid dementia, 2 cases of neurosyphilis paralytic dementia cases, 4 cases of dementia after hydrocephalus, 1 case of dementia after heavy metal poisoning, 3 cases of dementia after organic pesticide poisoning, 6 cases of dementia after intracranial infection, and 9 cases of mixed dementia. Another 7 patients did not meet the criteria for diagnosing dementia according to international standards, and the clinical data of 14 patients were incomplete. Of the 68 patients diagnosed with AD, 6 patients had incomplete data or lost contact during the follow-up of this study (Figure 1 provides a schematic diagram of the process for selecting patients). The clinical diagnostic criteria of AD are verified in accordance with the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association. Among the 62 patients with complete follow-up of AD, 7 had a family history of dementia, including 4 with *APP* gene mutation, 2 with *PS-1* gene mutation, and 1 with *PS-2* gene mutation.

The 62 patients in this follow-up study were 55 to 92 years old (71.0 years old \pm 8.7 years old), 24 males and 38 females. All of them had chronic insidious onset and were sent to the hospital for treatment after they were found to have abnormal symptoms by their families. These patients had no history of major mental trauma, no history of head trauma, no history of drug abuse and toxicosis. The first symptoms were as follows: 19 cases (30.6%) of memory loss, 15 cases (24.2%) of personality changes, and 28 cases (45.1%) of abnormal mental behavior. The time from onset to hospital admission ranges from 5 d to 1.5 years. Initially, 35 patients (56.5%) were misdiagnosed as depression, schizophrenia, personality disorder, menopausal syndrome, affective psychological disorder and insomnia, *etc.* Throughout the course of the disease, all patients had obvious clinical manifestations of memory loss and abnormal mental behavior. The 54 patients had obvious short-term memory deficits, 34 patients had abnormal personality, 26 patients hallucinated, 20 patients had significant depression, 19 patients had persecuted delusions, 12 patients had autonomic dysfunction, and 10 patients

had varying degrees of consciousness disturbances, including special disturbances of consciousness, delirium, and stupor. Follow-up was interrupted for 6 patients, two of whom died of complicated pneumonia and respiratory failure, one of whom died of complicated lung cancer metastasis and spread, one of whom died of complicated arrhythmia, and two of whom had family members who were unwilling to cooperate with follow-up. The clinical characteristics and other basic information of the AD patients studied were summarized (Table 1).

Auxiliary inspection results

The data of Cranial MRI, MRS, EEG, blood routine, and blood immune cell tests were available for all patients. There were 52 cases with abnormal brain MRI, including 43 (69.4%) with brain atrophy, 22 (35.5%) with demyelinating lesions around the ventricle (white matter osteoporosis), and 36 (25.8%) with abnormal T2 signals in the hippocampus (Figure 2). There were 60 cases with abnormal brain MRS, including 59 cases with decreased NAA/Cr (95.1%) and 56 cases with increased MI/Cr (90.3%). There were 48 cases (77.4%) with abnormal EEG examination, including 18 patients with high-amplitude β waves, 17 patients with more theta waves, 13 patients with δ waves, and the ratio of $(\theta + \delta)/(\alpha + \beta)$ is greater than 1.8 in 42 patients. Among the AD patients in this study, only 5 patients had mild abnormalities in routine blood tests, while the NLR value exceeded 4.5 in 20 patients and exceeded 4.0 in 46 patients. Blood immune cell examination found abnormal in 38 cases, mainly the proportion of T lymphocytes or NK cells decreased. The proportion of T lymphocytes was $(55.4\% \pm 6.3\%)$ in AD patients. The partial results of detecting lymphocyte subsets using flow cytometry are shown in Figure 3.

The relevant situation of the treatment effect

All patients were treated with medications, mainly medications that may improve cognitive function. Among them, 48 patients were treated with Donepezil (5-10 mg/d), 7 patients were treated with nicergoline, 5 patients were treated with Galantamine. Huperzine A was used in 2 cases. In addition, piracetam, oxiracetam, adenosine triphosphate, coenzyme Q10, vitamin E and other drugs were used for treatment. Risperidone, or olanzapine, or clozapine was used at the same time to control mental symptoms. All patients were not treated with transcranial magnetic therapy, acupuncture therapy, music therapy, psychotherapy, and other treatment methods. The average follow-up time is 10 months (6-24 months). At the end of the follow-up, 16 patients (25.8%) had a good prognosis, 19 patients (30.6%) had a moderate prognosis, and 27 patients (43.6%) had a poor prognosis. mRS score: 5 points for 3 cases, 4 points for 7 cases, 3 points for 4 cases, 2 points for 17 cases, 1 point for 23 cases, and 0 points for 8 cases. Among them, 28 cases were treated with risperidone alone to control their psychiatric symptoms, and the follow-up mRS score was 1-5 (3.00 ± 0.72) points. Four patients died during the follow-up period, and 40 patients were hospitalized again during the follow-up period.

Prognosis and predictive factors

Univariate analysis showed that there were significant differences in five indexes in the corresponding auxiliary examination test values between the groups with good prognosis and poor prognosis, including hallucination ($P = 0.025$), abnormal EEG ($P = 0.003$), the ratio of $(\theta + \delta)/(\alpha + \beta)$ by EEG ($P = 0.019$), abnormality of hippocampus ($P = 0.001$), the proportion of T lymphocytes obtained by flow cytometry ($P = 0.008$). We found that the proportion of T lymphocytes $< 55\%$ can be used as the cut-off threshold for predicting the poor prognosis of AD. We also found that the ratio of $(\theta + \delta)/(\alpha + \beta)$ was usually greater than or equal to 1.8 in the poor prognosis group. In addition, patients with severe depressive symptoms, moderate or severe brain atrophy, severe abnormal EEG, and significantly reduced ratios of T lymphocytes or NK cells were associated with poor prognosis in AD patients (Tables 2 and 3).

The NLR ratio in blood, the severity of memory impairment and the time of drug treatment had no significant correlation with the prognosis of AD patients. The ROC analysis of NAA/Cr obtained by MRS can predict the adverse prognosis of AD patients, and the area under the curve is 0.825 (95% confidence interval: 0.126-0.958; $P < 0.01$). According to the ROC curve, the best intercept value is 1.52, the sensitivity is 85.6%, and the specificity is 89.3% (Figure 3). Subsequently, spearman correlation analysis or the Rank Sum test was performed. The correlation between the NAA/Cr ratio and mRS score after the treatment of donepezil in 28 patients was analyzed, and it was found that there was a positive correlation between the two group ($r = 0.609$, $P < 0.05$); the number of days of donepezil treatment to improve cognitive function was negatively correlated with mRS score ($r = 0.578$, $P < 0.05$).

DISCUSSION

In this project, we retrospectively studied the subsequent prognosis of patients initially diagnosed with AD. We analyzed the clinical features, blood examination results, imaging data, EEG results and flow cytometry results. It also focused on the factors that are closely related to the poor prognosis. This study showed that the median T lymphocyte percentage in the poor prognosis group was significantly lower than that in the good prognosis group. The percentage of T lymphocytes in the blood to the total lymphocytes is an important indicator reflecting the cellular immune function. There have been studies by scholars supporting that reduced cellular immune function may promote the onset of AD[21], our research results suggest that the reduced cellular immune function further makes the prognosis of AD patients worse. T lymphocytes are the main cells of cellular immunity. After being stimulated by antigens, T lymphocytes transform into sensitized T cells. They have direct killing effect on the invading antigen and the synergistic killing effect of cytokines released by sensitized T cells[22,23]. In anti-infective immunity, cellular immunity is the main force of anti-infective immunity to participate in immune protection. In neurodegenerative diseases, the decrease of cellular immune function is more likely due to the reduction of the body's own immunity[24]. After a transgenic AD mouse lacking T lymphocytes

Table 1 Clinical data and related characteristics of the Alzheimer's disease patients

Characteristics	Patients
Sex (male/female)	24/38
Age, mean, range (yr)	71 (55-92)
Interval between onset and hospitalization	87, 5-547
Mean, range (d)	
Initial symptom	
Hypomnesia, <i>n</i> (%)	19 (30.6)
Apparent personality change	15 (24.2)
Abnormal mental behavior	28 (45.1)
Personality abnormality, <i>n</i> (%)	34 (54.8)
Recent memory deficits, <i>n</i> (%)	54 (87.1)
Hallucination, <i>n</i> (%)	26 (41.9)
Delusion of victimization, <i>n</i> (%)	19 (30.6)
Disturbance of consciousness, <i>n</i> (%)	10 (16.1)
Depressed, <i>n</i> (%)	20 (32.2)
Abnormal EEG results, <i>n</i> (%)	48 (77.4)
$(\theta + \delta)/(\alpha + \beta)$ more than 1.8, <i>n</i> (%)	42 (67.7)
Abnormal brain MRI results, <i>n</i> (%)	52 (83.9)
Encephalatrophy, <i>n</i> (%)	43 (69.4)
Abnormality of hippocampus, <i>n</i> (%)	36 (58.1)
Ratio of NAA/Cr decreased, <i>n</i> (%)	59 (95.2)
NLR (median interquartile)	2.25 (1.59-2.97)
Proportion of T lymphocytes in blood	0.55 (0.47-0.63)
Proportion of B lymphocytes in blood	0.13 (0.09-0.18)
Proportion of NK cell in blood	0.11 (0.07-0.17)

EEG: Electroencephalogram; MRI: Magnetic resonance imaging; NLR: Neutrophil-to-lymphocyte ratio; NAA: N-acetylaspartate; Cr: Creatine; NK: Natural killer.

was cultured for 6 months, Marsh *et al*[25] found that the accumulation of beta amyloid in the brains of these mice was more than twice that of AD mice with intact immune systems. In addition, the neuroinflammation of Rag5xfad mice with immunodeficiency was significantly increased, which is manifested by changes in the phenotype of microglia, increased production of cytokines, and decreased phagocytic ability. Regulatory T cells are important factors in maintaining immune tolerance of the body, and they may have a protective effect on the pathogenesis of AD[17]. It is speculated that the decline of cellular immune function is not only closely related to the onset of AD, but also has a greater relationship with the poor prognosis of AD. There is increasing evidence that the occurrence of AD is closely related to slow immune inflammation, and the changes of lymphocytes in the blood may be directly related to this slow immune inflammation. Therefore, in this study, data from lymphocyte subsets were collected and analyzed.

MRS is an imaging technique that uses the principle of magnetic resonance and chemical shift phenomena to perform imaging and quantitative analysis of specific nuclei and related compounds[26,27]. In the normal human brain, there are 5 resonance spectrum peaks in the MRS examination: NAA peak, Cho peak, Cr peak, inositol peak, and glutamate peak. The decrease in NAA peak can be used as a sign of neuron loss or damage in the brain. The content of Cr in the gray matter of the brain is higher than that of the white matter, and it is a high energy phosphoric acid reserve substance for ATP/ADP conversion[28]. This research found that the NAA/Cr ratio of the AD poor prognosis group was significantly lower than the NAA/Cr ratio of the good prognosis group. The decrease in NAA/Cr ratio indicates that there is more loss of bilateral hippocampal neurons, which can be used as a biomarker for the transition from mild cognitive impairment to AD. Zhang *et al*[29] found that the NAA/Cr ratio of the posterior cingulate gyrus of MCI patients who progressed to AD dementia was lower than that of patients who progressed to Lewy body dementia (DLB). The prognosis of AD type dementia and DLB. Kantarci *et al*[30] tested the cranial MRS of AD, VD, and DLB patients and found that NAA/Cr in AD and VD patients were lower than normal. AD patients had NAA/Cr lower than DLB patients. The

Table 2 Univariate analysis of prognostic factors associated with Alzheimer's disease

Variables	Good prognosis (n = 27)	Poor prognosis (n = 35)	P value
Age (yr)	71.2 ± 15.3	70.6 ± 16.7	0.829
Sex, n (%)			
Male	11 (40.7)	15 (42.9)	0.867
Female	16 (59.3)	20 (57.1)	
Duration from onset to admission, n (%)			
< 90 d	18 (66.7)	22 (62.9)	0.755
≥ 90 d	9 (33.3)	13 (37.1)	
Personality abnormality			
Yes	15	19	0.092
No	12	16	
Recent memory deficits			
Yes	22	32	0.247
No	5	3	
Hallucination			
Yes	7	19	0.025
No	20	16	
Delusion of victimization			
Yes	5	14	0.069
No	22	21	
Disturbance of consciousness			
Yes	2	8	0.101
No	25	27	
Depressed			
Yes	8	12	0.698
No	19	23	
Abnormal EEG results			
Yes	16	32	0.003
No	11	3	
($\theta + \delta$) / ($\alpha + \beta$) from EEG			
≥ 1.8	14	28	0.019
< 1.8	13	7	
Abnormal brain MRI results			
Yes	24	28	0.346
No	3	7	
Encephalatrophy			
Yes	20	23	0.479
No	7	12	
Abnormality of hippocampus			
Yes	8	28	0.001
No	19	7	
NAA/Cr ratio decreased			

Yes	25	34	0.408
No	2	1	
NLR (median IQR)	2.19 (1.51-2.87)	2.34 (1.62-3.28)	0.379
Proportion of T lymphocytes in blood	0.63 (0.38-0.77)	0.37 (0.24-0.49)	0.008
Proportion of B lymphocytes in blood	0.11 (0.08-0.18)	0.14 (0.10-0.23)	0.282
Proportion of NK cell in blood	0.15 (0.08-0.19)	0.10 (0.06-0.16)	0.075

AD: Alzheimer’s disease; SD: Standard deviation; IQR: Interquartile range; EEG: Electroencephalogram; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; NLR: Neutrophil-to-lymphocyte ratio; NAA: N-acetyl aspartate; Cr: Creatine; NK: Natural killer. *P* values < 0.05 are considered statistically significant.

Table 3 Multivariate analysis of factors associated with a poor prognosis			
Variables	OR	95%CI	P value
Hallucination	2.961	0.265-18.397	0.723
Abnormal EEG results	1.983	0.079-7.531	0.682
Abnormal brain MRI results	12.369	0.592-39.127	0.849
Abnormality of hippocampus	5.394	0.275-78.364	0.231
NAA/Cr ratio decreased	1.398	0.056-135.284	0.816
Proportion of T lymphocytes in blood	3.265	1.156-5.681	0.038

95%CI: 95% confidence interval; OR: Odds ratio; EEG: electroencephalogram; NAA: N-acetylaspartate; Cr: Creatine.

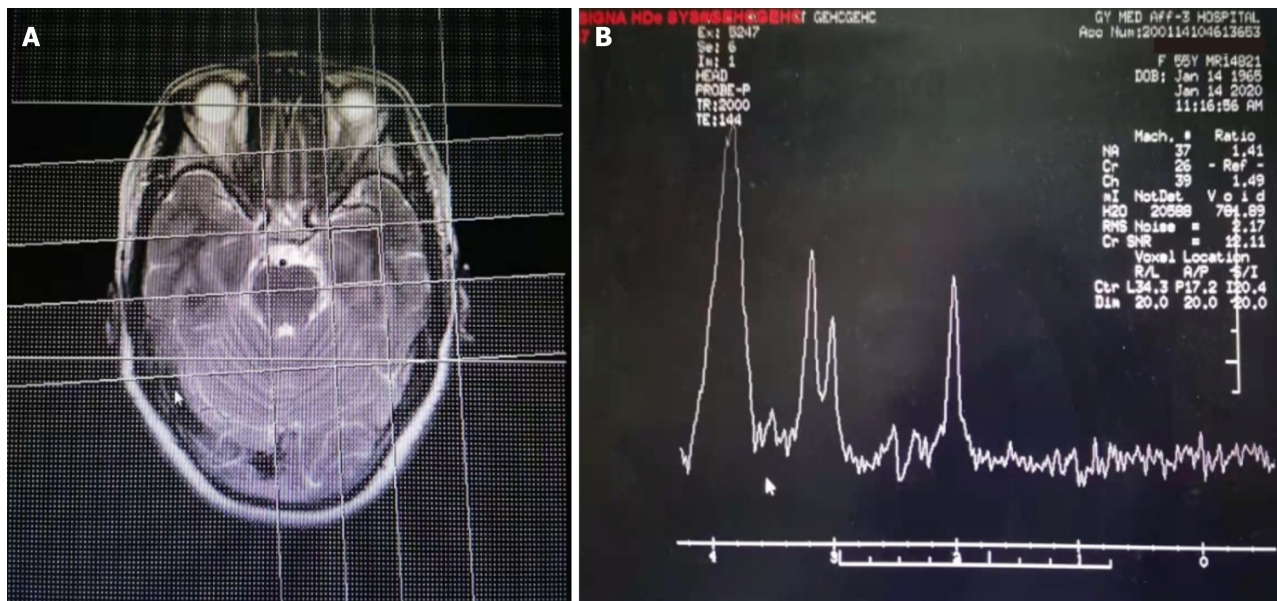


Figure 2 Magnetic resonance imaging and corresponding magnetic spectroscopy images of an Alzheimer’s disease patient. The patient was a 55-year-old female with a 4-year course of disease and a Mini Mental State Examination Scale score of 14 points. A: Magnetic resonance imaging images (axial view) of the patient showed mild degeneration and atrophy in the hippocampus, deepening of multiple cerebral sulcus, suggesting mild brain atrophy; B: The corresponding magnetic spectroscopy pictures of the patient showed N-acetylaspartate 37mmol/L, creatine 26 mmol/L, and choline 39 mmol/L, indicating that there was a metabolic disorder of brain neurotransmitters.

Cho/Cr ratio of AD and DLB patients was higher than normal. The researcher believes that in dementia characterized by neuronal loss, NAA/Cr ratio is reduced, and in dementia characterized by severe cholinergic insufficiency, Cho/Cr ratio is elevated. By examining the cranial MRS of AD patients, it can not only be used to diagnose AD, but also be used to evaluate the prognosis of AD patients.

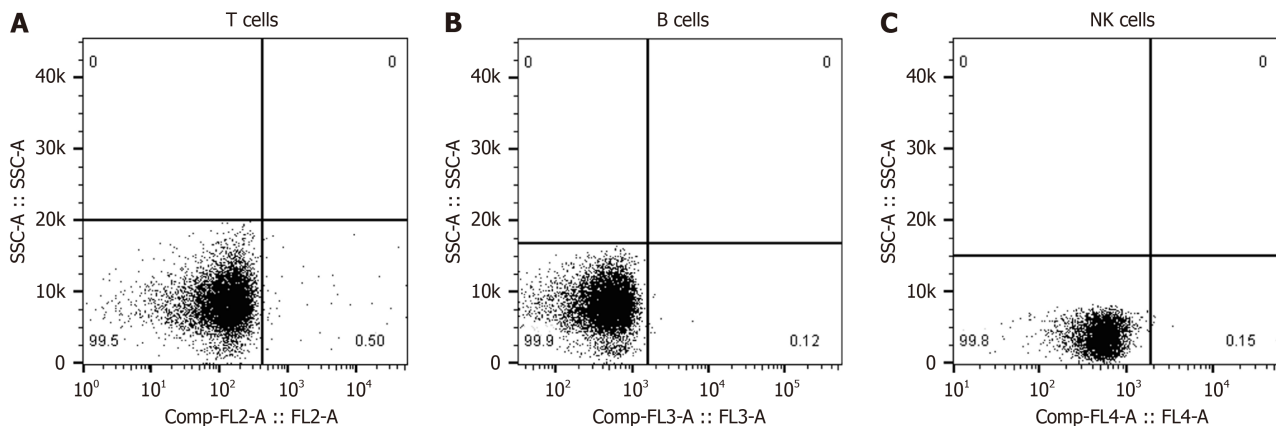


Figure 3 Lymphocyte subsets in the blood of Alzheimer's disease patients were detected by flow cytometry. A: T cell was detected by using Anti-human CD3e-PE (ebioscience); B: B cells were detected by using Anti-Human CD19-PerCP (BioLegend); C: Natural killer cells were detected by using anti-human CD56-APC (ebioscience). NK: Natural killer.

EEG examination is mainly used for differential diagnosis of epilepsy, as well as auxiliary diagnosis of encephalitis and certain encephalopathy[31]. This study also found that the prognosis of AD patients with a ratio of $(\theta + \delta)/(\alpha + \beta)$ greater than or equal to 1.8 obtained by EEG was poor, suggesting that careful EEG analysis also has a certain value in judging the prognosis of AD. Engedal *et al*[32] used statistical pattern recognition quantitative EEG to predict the conversion rate of dementia in patients with subjective cognitive decline (SCD) and MCI, and conducted follow-up. Of the 200 participants with complete data, 70 cases progressed from other conditions to dementia, and 52 cases developed to AD. Based on the EEG test results, the receiver operating characteristics analysis showed that the area under the curve was 0.78, the corresponding sensitivity was 71%, and the specificity was 69%. Researcher believe these SCD and MCI patients are at high risk of developing dementia within five years. Our study also found that the clinical prognosis of AD patients with severe depressive symptoms, moderate or severe brain atrophy, and severe abnormal EEG is poor. These aspects need to be grasped as a whole and further analyzed. Olichney *et al*[4] believed that when abnormal N400 and P600 repeat effects were detected by cognitive event related potential (ERP) in AD patients, it indicated that the synaptic plasticity in the brain of the patients had been significantly abnormal. Abnormalities of P600 or N400 in MCI patients are significantly associated with an increased risk of subsequent conversion to AD, and ERP test could provide a useful biomarker for the diagnosis of AD patients.

NLR is considered to be an easy to detect and operate systemic inflammatory index, which is related to the abnormal cellular immune function. Based on the above considerations, we analyzed the impact of NLR on the prognosis of AD patients. The results showed that there was no significant correlation between the ratio of NLR in blood and the prognosis of AD patients. Rembach *et al*[33] found that the sensitivity of NLR itself is not enough to diagnose AD. There is indeed a certain correlation between NLR and neocortical amyloid load in the cross section, but this relationship disappeared after longitudinal analysis. Moreover, the association between NLR and cognitive decline is also limited. They believe that NLR may only reflect the peripheral blood related inflammatory process, which is greatly affected by age and gender. These research results and views are basic consistent with our conclusion. Under normal circumstances, a small number of activated T cells enter the brain and participate in immune monitoring, but the infiltration of a large number of T cells usually occurs in the case of severe chronic immune inflammation in AD. Macrophages rather than microglia are the main phagocytes in the brain. These infiltrating cells are the key to the repair process. Giving anti-inflammatory treatment at the appropriate time of the disease can reduce the risk of A β pathological damage caused by deposition[34-36].

However, our research had some limitations. First, this study was a retrospective analysis, and it is difficult to control confounding factors. Second, the items related to the detection of cellular immune function were incomplete, and lymphocyte transformation test and immunoglobulin test were not carried out. Third, the sample size of this study is relatively small, and it is a single institution study, and the popularization value of the conclusion is limited. Nevertheless, this research still has some valuable findings in predicting the correlation between abnormal cellular immune function and poor prognosis in AD patients.

CONCLUSION

The decrease in the proportion of T lymphocytes may have predictive value for the poor prognosis of AD (Figure 4). It is suggested that the proportion of T lymphocytes less than 55% should be used as the cut-off threshold for predicting the poor prognosis of AD. In addition, MRS combined with EEG detection is also worthy of recognition in predicting the poor prognosis of AD. Yet the early and continuous drug treatment that improve cognitive function is associated with a good prognosis.

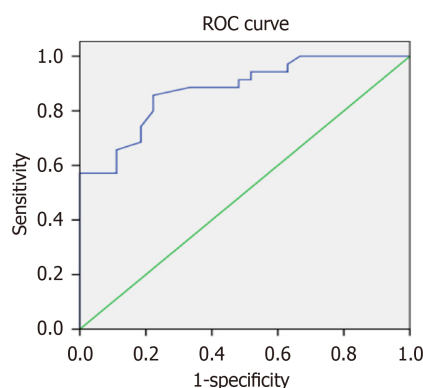


Figure 4 Receptor working curve of the predictive value of N-acetylaspartate/creatine ratio of magnetic spectroscopy for poor prognosis of Alzheimer's disease. ROC: Receptor working curve.

ARTICLE HIGHLIGHTS

Research background

Alzheimer's disease (AD) is a neurodegenerative disease with severe cognitive dysfunction. The prominent clinical manifestations are memory loss, confusion of thinking and logic, and abnormal mental behavior. At present, it is also inclined to think that AD is a chronic inflammatory disease mediated by abnormal autoimmune function. Mononuclear RNA sequencing and transcriptomics analysis show that the abnormal changes in microglia in the brain of AD patients induce a series of abnormal immune function. The activation of abnormal inflammasome represented by nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor protein 3 (NLRP3) inflammasome mediates the secretion of many immune inflammatory factors and subsequent cascades of chronic cascades reactions in immune inflammation. The amyloid β ($A\beta$) peptide produced by abnormal neurons precipitates and aggregates outside the cell. The hyperphosphorylation of tau protein can also easily cause aggregation, leading to neuron and nerve synaptic dysfunction and cell death, especially small glial cells. Reactive proliferation of glial cells often causes secondary cytopathological reactions in diseased brain regions.

Research motivation

The role of chronic immune inflammation in the pathogenesis of AD is becoming more and more important. The ratio of NLR in blood is an important systemic inflammatory biomarker. NLR is calculated by absolute counting of neutrophils divided by absolute counts of lymphocytes. NLR has been reported to be increased in diabetes, hypertension, myocardial infarction, stroke and some tumor patients, which may be a new index to evaluate the prognosis of these patients. The detection of T lymphocytes, B lymphocytes and natural killer cells in blood by flow cytometry can evaluate whether the immune function of AD patients is abnormal. Combined with the detection of relevant biochemical markers and EEG wave indexes by cranial magnetic spectroscopy (MRS), it has great clinical significance for the early diagnosis and prognosis evaluation of AD patients. As far as we know, little research work has been carried out in this regard.

Research objectives

To explore the correlation between abnormal immune function and adverse prognostic factors in AD patients, and hope to find some valuable clues.

Research methods

A retrospective analysis of 62 hospitalized patients clinical diagnosed with AD who were admitted to our hospital from November 2015 to November 2020. Collect cognitive dysfunction performance characteristics, laboratory test data and neuroimaging data from medical records within 24 h of admission, including MMSE score, drawing clock test, blood T lymphocyte subsets, and NLR, disturbance of consciousness, extrapyramidal symptoms, electroencephalogram (EEG) and head nucleus MRS and other data. Multivariate logistic regression analysis was used to determine independent prognostic factors, the modified Rankin scale (mRS) was used to determine whether the prognosis was good. The correlation between drug treatment and prognostic mRS score was tested by the rank sum test.

Research results

Univariate analysis showed that abnormal cellular immune function, extrapyramidal symptoms, obvious disturbance of consciousness, abnormal EEG, increased NLR, abnormal MRS, and complicated pneumonia were related to the poor prognosis of AD patients. Multivariate logistic regression analysis showed that the decrease in the proportion of T lymphocytes in the blood after abnormal cellular immune function (odd ratio: 2.078, 95% confidence interval: 1.156-3.986, $P < 0.05$) was an independent risk factor for predicting the poor prognosis of AD. The number of days of donepezil treatment to improve cognitive function was negatively correlated with mRS score ($r = 0.578$, $P < 0.05$).

Research conclusions

The decrease in the proportion of T lymphocytes may have predictive value for the poor prognosis of AD. It is suggested that the proportion of T lymphocytes less than 55% should be used as the cut-off threshold for predicting the poor prognosis of AD. In addition, MRS combined with EEG detection is also worthy of recognition in predicting the poor prognosis of AD. Yet the early and continuous drug treatment that improve cognitive function is associated with a good prognosis.

Research perspectives

It is speculated that the decline of cellular immune function is not only closely related to the onset of AD, but also has a greater relationship with the poor prognosis of AD. There is increasing evidence that the occurrence of AD is closely related to slow immune inflammation, and the changes of lymphocytes in the blood may be directly related to this slow immune inflammation. In a word, this research still has some valuable findings in predicting the correlation between abnormal cellular immune function and poor prognosis in AD patients.

FOOTNOTES

Author contributions: Bai H contributed to study design, fundraising, and manuscript preparation; Bai H, Zeng HM, Hu YZ, and Deng FF contributed to investigation and data collection; Zeng HM, Zhang QF, and Bai H contributed to results analysis and discussion; all authors approved the final version of this manuscript.

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