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Original Article

Prognostic value of plasma Aβ1-40 for Alzheimer's disease

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Abstract: Objective: To investigate the clinical significance of plasma p-amyloid 1-40 (Aβ1-40) in patients with Alzheimer's disease (AD). Methods: In this retrospective study, the clinical data of 305 patients, with or without Alzheimer's disease (AD), who were treated at the Affiliated Hospital of Youjiang Medical University for Nationalities and the People's Hospital of Baise between January 2018 and December 2021 were analyzed. Patients were divided into two groups: an AD group (n=147) and a non-AD group (without AD, n=158 cases). Blood test indices, including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (CRE), high-sensitivity C-reactive protein (hsCRP), and plasma β-amyloid 1-40 were collected and compared between the two groups. Results: The plasma β-amyloid 1-40 in the AD group was (3.71±3.45) mol/L, which was significantly higher than (2.8±1.35) mmol/L in the non-AD group (P<0.05). Similarly, hsCRP expression was significantly higher in the AD group than that in the non-AD group (P<0.05). There were no significant differences in AST, ALT, UA, T-tau, NFL or Cr levels between the two groups (all P>0.05). Moreover, univariate regression analysis showed that plasma β-amyloid 1-40 and hsCRP were significantly correlated with AD. Multiple regression analysis demonstrated that plasma p-amyloid 1-40 (P<0.0001) and hsCRP (P=0.002) were independent predictors of AD. Conclusion: Plasma p-amyloid 1-40 and hsCRP are closely related to AD, and may serve as important clinical predictors of AD.

Keywords: Predictive value, plasma β-amyloid 1-40, Alzheimer's disease

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease associated with aging, characterized by cognitive impairment, decreased living ability, and behavioral disorders, which are often irreversible [1, 2]. Due to the high prevalence, strong concealment, and long course, AD poses a huge burden on both families and society. Early diagnosis of AD involves neuropsychological evaluation, biochemical marker detection, imaging detection, and gene detection [3, 4]. However, most patients do not exhibit obvious biochemical or imaging changes in the preclinical stage [5, 6]. Senile plaques in the brain are considered hallmark pathologic signs of AD [7, 8].

Plasma β-amyloid level can reflect the selective deposition of insoluble plaques in the brain, a hallmark of AD [9]. Several studies have established that the formation of senile plaques is a typical pathological feature of AD [10-12]. Amyloid beta peptide (Aβ) is associated with AD-related phenotypes, and a decrease in the plasma Aβ1-42/Aβ1-40 ratio is inversely correlated with neocortical amyloid burden [13]. Although significant changes in plasma Aβ levels have been observed in patients with AD, contrasting studies indicate no direct association between plasma Aβ levels and AD [14, 15]. Studies have shown that elevated levels of Aβ1-40 in the brain can lead to the formation of amyloid plaques, contributing to the progression of AD [16]. Additionally, Aβ1-40 has been found to be toxic to neurons, leading to cell death and cognitive decline. Therefore, the relationship between plasma Aβ1-40 levels and AD warrants further investigation.

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This study aims to analyze the predictive value of plasma β-amyloid 1-40 (Aβ1-40) in patients with AD, amidst the current lack of definitive clinical evidence.

Materials and methods

Study design and ethics

This retrospective study included 305 patients from the Affiliated Hospital of Youjiang Medical University for Nationalities and the People's Hospital of Baise in Baise, Guangxi, China, between January 2018 and December 2022. The participants were divided into two groups: AD group (n=147) and non-AD group (n=158 cases). This study was reviewed and approved by the Medical Ethics Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities and the People's Hospital of Baise.

Inclusion and exclusion criteria

The inclusion criteria: ① Patients diagnosed with AD according to the criteria set by the National Institute on Aging-Alzheimer's Association [17]; ② Patients aged ≥18 years; ③ Patients with no acute stroke or other serious cerebrovascular diseases; ④ Patients with no previous history of epilepsy; ⑤ Patients free from other neurological diseases; ⑥ Patients with complete basic information and laboratory examination data.

Exclusion criteria: ① Patients with a history of malignant tumor; ② Patients with primary aphasia-related behaviors; ③ Patients with a history of blood system diseases; ④ Patients with typical features indicative of frontotemporal dementia or dementia with Lewy bodies; ⑤ Patients with a history of liver, kidney, or heart disorder; ⑥ Patients with incomplete clinical data.

Data collection

Demographic and clinical characteristics, such as age, sex, previous medical history, physical examination, laboratory examination, and intervention-related data were collected. Blood test indices, including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid (UA), creatinine (Cr), high-sensitivity C-reactive protein (hsCRP), and plasma β-amyloid 1-40 were also collected.

Observation index

① Plasma β-amyloid 1-40: We assessed the plasma β-amyloid 1-40 levels in both groups. Fasting blood samples were collected between 09:00-11:00, and stored in tubes containing ethylenediaminetetraacetic acid (EDTA). The samples were centrifuged (1000 rpm, 4°C) for 15 min. After centrifugation, plasma was transferred into 1.5 ml Eppendorf tubes and stored at -80°C. Plasma Aβ1-40 was quantified using an ultra-sensitive single-molecule array (Simoa) (Quanterix, MA, USA) on an automated Simoa HD-X platform according to the manufacturer's instructions. The technicians who performed the assays were blinded to clinical data.

② Inflammatory index: The expression of high-sensitivity C-reactive protein (hs-CRP) was detected using enzyme-linked immunosorbent assay. HsCRP kits were provided by Everbright Biotechnology Co., Ltd. The procedures were performed in strict accordance with the operating manual. Liver and kidney function serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid (UA), and creatinine (Cr) levels were measured using Beckman Coulter AU5800 devices according to the manufacturer's guidelines for clinical laboratory investigations.

Statistical analysis

All data in this study were confirmed by at least two medical staff before being entered into computer. All data in this study were processed using SPSS software (version 19.0). The measurement data were expressed as (Mean ± SD), and the comparisons between the two groups was performed using independent t-test while the comparison within a group before and after the intervention was compared using paired t-tests. The count data were expressed as percentages (%), and compared by χ^2 test. The multivariate regression analysis was conducted to identify the independent risk factors for AD. The predictive value of plasma β-amyloid 1-40 for AD were analyzed using the receiver operating characteristic curve (ROC). Statistical significance was set at $P<0.05$.

Results

Clinical data of the participants

The mean age of the AD group was (72.43± 11.16) years old and that of the non-AD group

Table 1. Clinical characteristics of two groups

	AD group (n=147)	Non-AD group (n=158)	t/χ^2	P
Age (years)	72.43±11.16	64.12±9.573	2.25	0.55
Sex			4.68	0.58
Male (n%)	77 (52.4%)	80 (50.6%)		
Female (n%)	70 (47.6%)	78 (49.4%)		
BMI	21.2±3.65	23.25±4.29	1.39	0.24
Smoking	130 (88.4%)	31 (19.6%)	6.71	0.55
Cerebral infarction	24 (16.3%)	13 (8.2%)	2.96	0.42
Hypertension	58 (39.5%)	84 (53.2%)	1.79	0.16
Diabetes	20 (13.6%)	12 (7.6%)	1.29	0.49
Coronary heart disease	15 (10.2%)	7 (4.4%)	2.98	0.12

Note: BMI: body mass index.

Table 2. Comparison of liver and kidney function between two groups ($\bar{x}\pm s$)

Group	AST	ALT	UA	Cr	Plasma β-amyloid 1-40	T-tau	NFL
AD group (n=147)	28.35±26.17	22.5±25	370.85±146	113.21±67.94	3.71±3.45	3.76±2.22	7.77±2.35
Non-AD group (n=158)	22.73±12.57	25.69±38.33	327.03±96.26	79.18±20.36	2.8±1.35	3.66±2.19	7.56±2.09
t	1.278	2.131	1.921	4.549	6.989	2.098	3.987
P	0.63	0.45	0.06	0.19	0.02	0.187	0.096

Note: AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; UA: Uric Acid; Cr: creatinine; NFL: neurofilament light; T-tau: total tau.

Table 3. Comparison of inflammatory index between two groups ($\bar{x}\pm s$)

Group	hsCRP	Neutrophil ratio (%)
AD group (n=147)	35.02±57.91	67.91±13.04
Non-AD group (n=158)	14.73±27.29	63.03±12.64
t	6.578	2.131
P	0.01	0.25

Note: hsCRP: high sensitivity C-reactive protein.

was (64.12±9.573) years old (P>0.05). The BMI in the AD group and the non-AD group was (21.2±3.65) kg/m^2 and (23.25±4.29) kg/m^2, respectively (P>0.05). Besides, there were no significant differences between the two groups in terms of history of smoking, hypertension, diabetes, coronary heart disease, or cerebral infarction (all P>0.05) (**Table 1**).

Liver and kidney function and plasma β-amyloid 1-40 level

The AST, ALT, UA, T-tau, NFL, and Cr levels in the AD group were (28.35±26.17) mmol/L, (22.5±25) mol/L, (370.85±146) mmol/L, (3.76±2.22) pg/ml, (7.77±2.35) pg/ml and (113.21±67.94) mmol/L respectively, whereas those in the non-AD group were (22.73±12.57) mmol/L, (25.69±38.33) mmol/L, (327.03±96.26) mmol/L, (3.66±2.19) pg/ml, (7.56±2.09) pg/ml and (79.18±20.36) mmol/L, respectively (all P>0.05). The plasma β-amyloid 1-40 in the experimental group was (3.71±3.45) mol/L, and that in the control group was (2.8±1.35) mmol/L (P<0.05) (**Table 2**).

Inflammatory index

As shown in **Table 3**, hsCRP level in the AD group was significantly higher than that in the control group (P<0.05). However, the neutrophil ratio was not significantly different between the two groups (P>0.05).

Univariate regression analysis of risk factors for AD

Univariate analysis showed that plasma β-amyloid 1-40 and hsCRP were significantly correlated with AD (all P<0.05), whereas age, BMI, cerebral infarction, hypertension, diabetes, coronary heart disease, AST, ALT, Ur, and UA were not significantly correlated with AD (all P>0.05) (**Table 4**).

Table 4. Univariate analysis

Indexes	Rho	P
Age	-0.071	0.454
BMI (kg/m^2)	-0.070	0.461
Smoking	0.556	0.051
Cerebral infarction	-0.043	0.743
Hypertension	0.557	0.076
Diabetes	0.428	0.088
Coronary heart disease	0.458	0.054
Plasma β-amyloid 1-40	0.431	<0.001
AST	0.098	0.105
ALT	-0.072	0.101
UA	0.439	0.211
Ur	0.864	0.343
hsCRP	0.764	<0.001
Neutrophil ratio	0.546	0.33
T-tau	0.088	0.095
NFL	0.556	0.078

Note: The Pearson correlation analysis was used for normally distributed data, and the Spearman correlation analysis method was used for non-normally distributed data. BMI: body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; UA: Uric Acid; Cr: creatinine; hsCRP: high-sensitivity C-reactive protein; NFL: neurofilament light; T-tau: total tau.

Multivariate regression analysis of risk factors for AD

Multivariate regression analyses were conducted to screen the independent risk factors for the occurrence of AD. Plasma β-amyloid 1-40 and hsCRP, which had a significant correlation with AD in the univariate analysis, were taken as independent variables, while AD was taken as the dependent variable. Multivariate analysis revealed that plasma β-amyloid 1-40 (P<0.0001) and hsCRP (P=0.002) levels were independent predictors of AD occurrence (**Table 5** and **Figure 1**).

Discussion

The etiology and pathogenesis of Alzheimer's disease (AD) remain unclear. Currently, the diagnosis of AD relies on a detailed medical history, cognitive function examination, physical examination, and relevant laboratory tests, including brain CT, PET, and brain electrical activity mapping [18]. Although many researchers are trying to identify specific markers of AD, there is still a lack of universally accepted biological index for solid diagnosis. Histopathological examination, identifying specific neurotic plaques and neurofibrillary tangles, remains the gold standard for confirming AD [19]. Although brain tissue biopsy can provide an important basis for AD diagnosis, it is impractical for routine clinical practice use. Therefore, it is important to identify biological indicators outside the central nervous system to diagnose AD early [20].

Our study demonstrated that plasma β-amyloid 1-40 had an obvious predictive value for AD. The plasma β-amyloid 1-40 in the AD group was significantly higher than that in the non-AD group ((3.71±3.45) mol/L vs (2.8±1.35) mmol/L). Moreover, multivariate regression analysis demonstrated that plasma β-amyloid 1-40 level was an independent predictors of AD. Extensive research has confirmed inflammatory pathological changes in the brains of AD patients, and recent in vitro and in vivo studies have shown that the abnormal expression of plasma β-amyloid may activate an inflammatory response, continuously activating inflammatory repair mechanisms and transforming the acute response under normal conditions into chronic inflammatory injury [21-23]. Glial cells and their inflammatory products (IL-6, IL-8, hsCRP, and TNF-α) mediate this pathological injury process, which in turn promote the production of other inflammatory molecules by acting on glial cells or neurons [24]. This cascade contributes to the formation of chronic inflammatory reactions and a continuous increase in the levels of inflammatory factors, which have a wide range of effects on nerve growth and neural plasticity [25].

In AD, liver and kidney play important roles in the clearance and metabolism of various substances, including amyloid beta (Aβ) peptides [26]. Aβ peptides, which are produced in the brain and accumulate to form characteristic disease plaques, are metabolized and cleared from the blood by the liver. Aβ peptides are broke into smaller fragments that can be excreted from the body through the urine. Dysfunction in liver function can lead to reduced clearance of Aβ peptides, resulting in their accumulation in the brain [27]. Similarly, the kidneys contribute to the clearance of Aβ peptides by filtering them from the blood and excreting them in the urine. Dysfunction in kidney can also contribute to the accumulation of Aβpeptides in the body.

Table 5. Multivariate regression analysis

Dependent variables	Independent variables	B	SE	β	*P* Value	b
AD	Plasma β-amyloid 1-40	0.323	0.043	0.533	<0.0001	-0.2887
	hsCRP	1.488	0.594	0.384	0.002	-0.3872

Note: B: nonstandard regression coefficient; SE: standard error; b: standardized regression coefficient; β: multiple correlation coefficient adjusted for degrees of freedom; AD: Alzheimer's disease; hsCRP: high-sensitivity C-reactive protein.

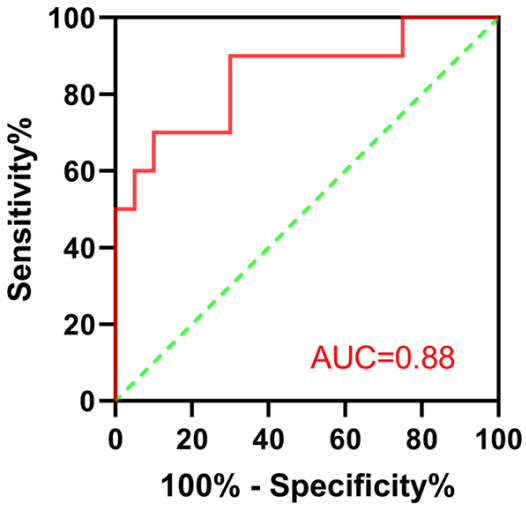

Figure 1. The ROC analysis of plasma β-amyloid 1-40 for the prediction of AD. AD: Alzheimer's disease; ROC: Receiver operating characteristic.

The results of this study showed that plasma hsCRP levels in the AD group were higher than those in the non-AD group, suggesting that inflammatory factors play an important role in the pathogenesis of senile AD. As the disease worsened, the expression of inflammatory factors increased. A study [28] has found that IL-1β, IL-6, and TNF-α can exacerbate inflammatory reaction and accelerate the impairment of microglia. Therefore, monitoring these inflammatory markers can assist clinicians in diagnosing and assessing the severity of AD in elderly patients.

Abnormal amyloid deposition and subsequent inflammation, neurodegeneration, and cell damage due to oxidative stress may also disrupt homeostasis, predominantly in the kidneys and other organs of patients with AD. Thus, renal clearance of amyloid decreases, resulting in enhanced amyloid toxicity [29]. However, in our study, we observed no differences in liver or kidney function between patients with and without AD. This may be because the accumulation of amyloid deposits did not significantly impair the liver or kidney function in our study subjects.

Our study has some limitations. First, this study was conducted at a single center and there was a certain selection bias. Second, its retrospective nature may also contribute to selection bias. Finally, the relatively small sample size necessitates validation through larger, more rigorous multicenter studies.

In conclusion, plasma β-amyloid 1-40 may be a novel and promising predictor of AD. Higher plasma β-amyloid 1-40 level are positively and strongly associated with AD.

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Written informed consent was received from both hospitals.

Disclosure of conflict of interest

None.

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