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Original Article

Evaluation of clinical efficacy of α-secretase in the treatment of Alzheimer's disease

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Abstract: Objective: To observe the improvement of α-secretase for the cognitive and living ability in patients with Alzheimer's disease. Methods: A total of 134 patients with Alzheimer's disease were randomly divided into 2 groups, each with 67 cases. The control group was treated with Donepezil Hydrochloride, and the observation group was treated with α-secretase therapy. The total course of treatment was 12 weeks, followed up every 4 weeks. Before and after treatment, the patients were evaluated with Alzheimer's Disease Assessment Scale-Cognitive section (ADAS-cog), the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) Rating Scale, and the Mini-Mental State Examination (MMSE), and were observed for the occurrence of adverse reactions. Results: Differences of various scores in patients between the two groups before treatment were not statistically significant (all $P>0.05$). After 12 weeks of treatment, the ADAS-cog score and BEHAVE-AD score of the observation group and the control group were all decreased (both $P<0.05$), and the MMSE scores were both increased ($P<0.05$). Improvements of the scores of each table in the observation group were more obvious than those in the control group and the differences of the two groups were statistically significant (both $P<0.05$). Expression levels of high-sensitivity C-reactive protein (HS-CRP) and interleukin-6 (IL-6) after treatment in the two groups were detected, and it was found that the HS-CRP and IL-6 expression before and after treatment in the observation group were significantly different (both $P<0.05$). Furthermore, expression of HS-CRP and IL-6 after treatment in the two groups was significantly different (both $P<0.05$). Conclusion: The use of α-secretase has a significant effect in the treatment of patients with Alzheimer's disease, and it can be popularized in clinical practice.

Keywords: α-secretase, Alzheimer's disease, high-sensitivity C-reactive protein, interleukin 6, randomized controlled

Introduction

Alzheimer's disease (AD) is one of the common diseases in the elderly, and the majority of clinical cases occur in elderly people. It is characterized by dementia, bluntness of reaction, and handicapped language function. As our country has entered the aging society, the government has begun to pay attention to the health problems of the elderly [1-3]. Some scholars have reported that the incidence of AD in patients over the age of 65 has increased exponentially. Additionally, the higher the age the higher the risk of AD [4]. Some studies also have shown that the prevalence of AD in patients over the age of 65 is as high as 7.2%. As a degenerative disease of the central nervous system, AD is mainly the degeneration of memory and cognitive ability after the onset of the disease, and it has caused great damage to the quality of life and mental state of the patients. However, clinical treatment methods and means for AD are less and the disease lacks a more ideal means. At present, the main treatment is Donepezil Hydrochloride tablets, but the treatment effect of this therapeutic method for long-term AD patients is not good enough and the prognosis is poor. Therefore, new classes of drugs are needed with better efficacy in the treatment of AD.

Amyloid precursor protein (APP) can produce soluble fragments of sAPPa by non-amyloid metabolism (α-secretase) [5]. A study has

Table 1. Clinical data of patients

Group	Observation group (n=67)	Control group (n=67)	χ^2/t	P
Gender			0.691	0.674
Male	37 (55.22)	35 (52.25)		
Female	30 (44.78)	32 (47.76)		
Age (year)			0.821	0.741
>65	42 (62.69)	47 (70.15)		
≤60	25 (37.31)	20 (29.85)		
White blood cell (10^9/L)	4.50±1.30	4.20±1.50	0.739	0.784
Hemoglobin (g/L)	152.00±24.00	147.00±33.00	0.574	0.847
Platelet (10^9/L)	129.00±27.00	138.00±21.00	0.833	0.736
BMI (kg/m^3)	20.10±1.20	21.10±0.95	0.530	0.812
Residence			1.644	0.517
Village	10 (14.93)	14 (20.90)		
City	57 (85.07)	53 (79.10)		
Education level			1.347	0.887
Below high school	15 (22.39)	13 (19.40)		
Not below high school	52 (77.61)	54 (80.60)		
Smoking			1.024	0.384
Yes	43 (64.18)	35 (52.24)		
No	24 (35.82)	32 (47.76)		
Alcohol abuse			0.742	0.629
Yes	12 (17.91)	8 (11.94)		
No	55 (82.09)	59 (88.06)		

Note: BMI, body mass index.

shown that sAPPa could effectively reduce the production of β amyloid protein, it has neurotrophic and protective effects, and this could inhibit the occurrence of AD [6]. In recent years, the treatment of α-secretase in patients with AD has been widely used with significant effect, which could improve the quality of life and mental state of patients. In this study, curative effect and clinical effect of α-secretase in AD were observed by detecting high-sensitivity C-reactive protein (HS-CRP) and interleukin 6 (IL-6) in peripheral blood of AD patients.

Materials and methods

General information

From March 2013 to February 2015, there were 134 cases of AD composed of 70 males and 64 females in The Third Affiliated Hospital of Zhengzhou University were collected, aged from 62 to 80 years with an average age of 68.4±8.1 years old. In this experiment, the patients were divided into two groups randomly, including 67 patients in the observation group, 37 males and 30 females, aged from 62 to 75 years, the average age 67.4±7.5 years old. Sixty-seven patients were in the control group, 35 males and 32 females, aged from 65 to 80 years, average age 69.7±6.6 years old. All the patients in this experiment met the diagnostic criteria of the 2011 edition of Neuropathic language apoplexy Institute of the American Congress (Alzheimer's Dementia). Detailed clinical data of the patients is shown in **Table 1**. This study was approved by the Medical Ethics Committee of The Third Affiliated Hospital of Zhengzhou University.

Inclusion criteria: Each patient was identified by two chief physicians and the course of the disease was more than 1 year. All patients had no respiratory system disease, liver and kidney dysfunction, diabetes and hypertension. All patients had complete clinical data, and all families were informed and signed informed consent.

Exclusion criteria: Recent blood transfusion treatment was carried out and patients were with hypersensitivity to Donepezil Hydrochloride tablets. Recently, drug therapy (benzodiazepines), radiotherapy and chemotherapy were carried out and patients had familial hereditary diseases and immunodeficiency or recent major accidents leading to intracranial damage.

Experimental methods

In this controlled trial, all patients were in strict accordance with the doctor's advice on life and diet control (taking a walk after meals; communicating more with the elderly; light diet avoiding spicy foods); patients of the control group took oral Donepezil Hydrochloride tablets (5 mg/tablet) once a day for treatment, under the guidance of the chief physician according to the clinical manifestations. The patients in the

Table 2. Comparison of the scores in patients of the two groups before and after treatment

Group	MMSE score	BEHAVE-AD score	ADAS-cog score
Observation group (n=67)			
Before treatment	12.88±3.67[a]	22.34±3.78[a]	36.64±3.47[a]
After treatment	23.62±2.01[b]	11.23±2.71[b]	27.67±3.19[b]
t	21.009	19.552	15.377
P	0.001	0.001	0.001
Control group (n=67)			
Before treatment	12.69±3.55	21.87±4.21	36.43±3.64
After treatment	20.36±2.64	14.35±3.20	21.67±3.28
t	14.191	11.640	24.962
P	0.001	0.001	0.001

Note: Compared with the control group before treatment, [a]P>0.05. Compared with the control group after treatment, t=10.73, [b]P<0.001. ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive section; BEHAVE-AD, the Behavioral Pathology in Alzheimer's Disease; MMSE, Mini-Mental State Examination.

observation group were treated with α-secretase (4-7 mg). The dosage was controlled by the clinician according to the clinical manifestations of the patients which could be appropriately changed with a continuous use for 12 weeks.

Detection of HS-CRP and IL-6 in peripheral blood

The day before treatment and the next day after treatment, the patients in the observation group and the control group maintained an empty stomach in the morning. Then 3-5 mL venous bloods of the patients were collected. Blood was collected with dry tube without anticoagulant, and was centrifuged at 5,000 rpm/min for 10 minutes. Automatic biochemical analyzer was used to detect and the expression level of HS-CRP was detected by immunoturbidimetry, and the expression amount of IL-6 in the serum was detected by radioimmunoassay.

Patient scores

In this experiment, the Mini-mental State Examination (MMSE) score was used to evaluate the response ability and intelligence status of patients with a total score of 30 points. The higher the score the higher the intelligence and the reaction energy. The rating scale of behavioral pathology in Alzheimer's disease (BEHAVE-AD) was used to evaluate the pathological behavior of AD patients with a total score of 30 points. The higher the score the more obvious the dementia symptoms. Alzheimer's disease assessment scale-cognitive section (ADAS-cog) score was used to evaluate the cognitive ability of the patients with the lower the score, the stronger the cognitive ability of patients. Patients with AD were evaluated by the above scales.

Statistical analysis

This study used SPSS 22.0 software package to carry out statistical analysis of the collected data. The count data are expressed by (n, %), and analysis was performed with the Chi-square test. Measurement data are expressed by mean ± standard deviation ($\bar{x}$ ± sd), and variance homogeneity test was adopted. If equal variance assumed, t test was used. Otherwise the rank sum test was used. Single-factor analysis was used in multi-group comparison. Statistical significance was judged as P<0.05.

Results

Clinical data analysis

Through the analysis of clinical data in patients of the two groups, it was found that differences between gender, age, white blood cell, hemoglobin, platelet, BMI index, place of residence, education level, eating habits, smoking, and alcohol abuse of the two groups were not statistically significant. (all P>0.05). See **Table 1**.

The scores of the patients in observation group and control group before and after treatment were compared

The patients' reaction ability and state of intelligence, pathological behavior and dementia symptoms were scored by three different grades, and it was found that there were no differences in MMSE, BEHAVE-AD, and ADAS-cog scores before treatment according to the treatments of two different dugs for the patients. There were no statistical differences between groups (all P>0.05). While after the treatment with Donepezil Hydrochloride tablets

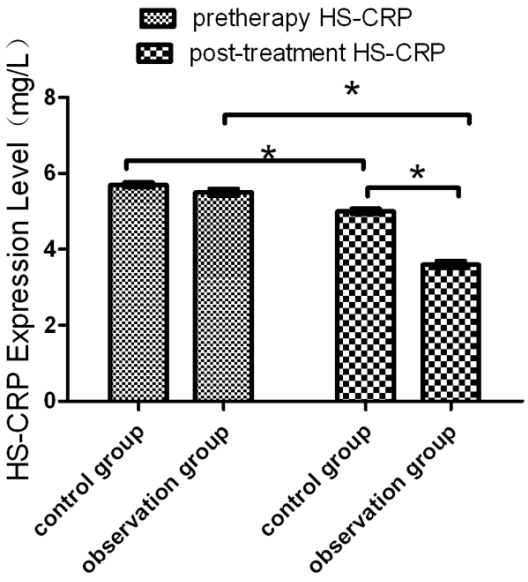

Figure 1. Expression level of HS-CRP in patients after treatment of the two groups. The venous bloods of the patients with empty stomach in the observation group and the control group were collected before and the next day after treatment in the morning. The expression level of HS-CRP inserum was detected by immunoturbidimetry. *P<0.05. HS-CRP, high-sensitivity C-reactive protein.

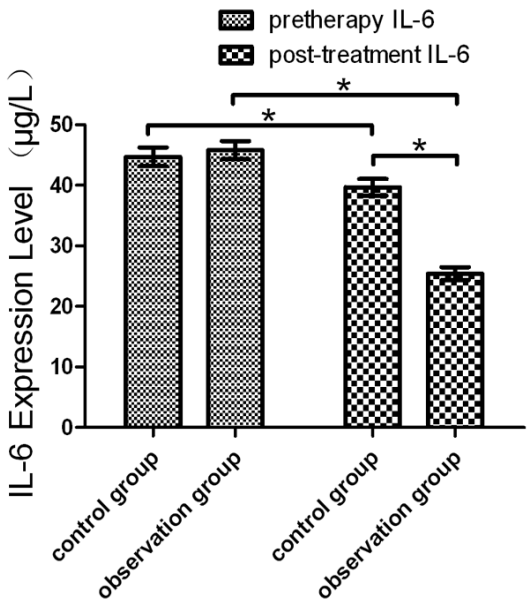

Figure 2. Expression level of IL-6 in patients after treatment of the two groups. The venous bloods of the patients with the empty stomach in the observation group and the control group were collected before and the next day after treatment in the morning. The expression level of IL-6 in serum was detected by radioimmunoassay. *P<0.05. IL-6, interleukin 6.

and α-secretase, the scores of the patients in the control group and the observation group were significantly improved. Compared with those before treatment, the differences were statistically significant (all P<0.05). Furthermore, the scores of the control group and the observation group after treatment were compared, and the results showed that the scores of the patients treated with α-secretase were significantly better than those of the control group. There were statistical differences (all P<0.05), as shown in **Table 2**.

Expression levels of HS-CRP and IL-6 in patients after treatment of the two groups

According to the detection of the expression of HS-CRP and IL-6, it was found that in patients of the control group, when the expression of HS-CRP (5.7±0.5 mg/L) and IL-6 (44.7±12.8 μg/L) before treatment were compared with those of HS-CRP (5.0±0.6 mg/L) and IL-6 (39.7±11.2 μg/L) after treatment, the expression was decreased and differences were statistically significant (both P<0.05). In patients of the observation group, when expression of HS-CRP (5.5±0.8 mg/L) and IL-6 (45.8±12.3 μg/L) before treatment were compared with those of HS-CRP (3.6±0.8 mg/L) and IL-6 (25.4±8.7 μg/L) after treatment, expression was decreased, and the differences were statistically significant (both P<0.05). Additionally, after treatment, expression of HS-CRP and IL-6 in the observation group were decreased, and the differences were statistically significant (both P<0.05). See **Figures 1**, **2**.

Discussion

Neuritic plaques accumulate in the brain of AD patients. The main component of the plaques is β amyloid, which is believed to be an important material for occurrence and development of AD [7-9]. When the metabolism of β amyloid is out of balance, it causes abnormal aggregation of protein, which will lead to a series of nerve damage in the brain, and then the memory and cognitive ability of the patients will be impaired [10]. Some studies have shown that β amyloid plaques are rich in a large amounts of inflammatory factors that stimulate glial cells to release a large number of inflammatory factors and inflammatory mediators to cause the death of the surrounding neurons. In these secreted

inflammatory factors, IL-6, and TNF-α are the main inflammatory factor signal proteins [11, 12]. IL-6 can further stimulate the activated receptor cells and promote the formation of β amyloid, thus lead to the aggravation of AD patients. CRP, as one of the extremely sensitive indicators of non-specific inflammatory response, is a protein mediated by IL-6 inflammatory factor, and is synthesized in hepatocytes. When the tissue is damaged, hypoxia-ischemia, trauma, and acute inflammation appear, and CRP in human blood will increase dramatically, and HS-CRP detects the expression of CRP in patients by a more sensitive standard [13-15]. In the study of Fuster et al., it was found that excluding the influence of other factors, the occurrence and development of chronic inflammation of neurons in the brain of the patients with AD can be directly reflected by the observation of the patient's HS-CRP [16].

In this study, a randomized controlled trial of 134 patients with AD was conducted, used two different drugs and evaluated the recovery of the patients. The two groups of patients' reaction ability and intelligence status, pathological behavior, dementia symptoms after treatment were scored. The patient's condition of two groups after treatment improved significantly compared with that before treatment. After treatment, the ADAS-cog score and BEHAVE-AD score of the observation group were lower than those of the control group, but MMSE score was obvious higher. This showed that the effect of treatment of AD by α-secretase was significant. Lichtenthaler et al. mentioned that α-secretase could effectively reduce neurotoxicity and the expression level of β amyloid, and protect the nerves by increasing sAPPa [17]. This study was corroborated by these results, and is given a more powerful confirmation of the reliability. Finally, the expression level of HS-CRP and IL-6 in the blood of the patients in two groups were detected, and it was found that two indexes in patients of two groups were all improved after treatment. Each index in the observation group by the treatment of α-secretase was better than that in the control group. This is because α-secretase is not an independent protease, and it has the ability to degrade the β amyloid sequence of APP molecules. It decomposed the APP in the cell membrane, caused the inhibition of hydroxamic acid as the first protease. This could effectively increase the secretion of sAPPa and reduce the expression level of inflammatory factors in patients, thus improving the patient's condition [18-20]. Treatment of AD patients by α-secretase could effectively improve the patient's condition, and has a significant effect on the recovery of memory ability of the patients.

However, there are still some defects existing in this study. In this study, further investigations for the occurrence and development of AD were not performed. Whether the lack of the samples can lead to deviation for this experiment is not known right now. Excessive use of α-secretase will also have a variety of side effects, and even more will lead to tumors, so strict control of the amount of α-secretase in clinical treatment is particularly critical. In the future research, in-depth study and discussion for the occurrence and development of AD will be performed and large sample data will be used to study the experiment, to ensure the validity and correctness of the experiment, to provide a good scheme for the clinical treatment of AD.

In summary, α-secretase has an obvious effect in the treatment of AD patients, which improves the patient's condition. It is worth utilizing in clinical practice.

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Disclosure of conflict of interest

None.

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