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Advances in Early Prevention of Alzheimer's Disease in the Aged

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease, is one of the leading causes of death in the aging population, and has become a serious public problem endangering the physical and mental health of the elderly. The disease not only affects the health of the elderly and the quality of life in their later years, but also brings heavy financial and emotional burden to the family and society. The specific mechanism of AD is still unclear, and the current treatments focus on improving mental function and slowing down memory loss. The early diagnosis of AD is difficult and there is no cure for it, so the early prevention is particularly important. This review will introduce the major treatment, potential risk factors and summarize the relevant research about early preventions of AD, such as regular physical sports, reasonable nutritional diet, certain social activities and so on, and expect to provide a new direction for the improvement of AD.

Keywords

Aged, Early Prevention, Alzheimer's Disease

1. Introduction

Overview of Alzheimer's Disease

Alzheimer's disease is the most common type of senile dementia, characterized by the failure of memory and dementia, the onset of the disease is insidious, and the course is chronic and progressive. At present, about 47 million people suffer from dementia worldwide [1]. According to the Report of World Alzheimer, it has been estimated that the number of AD patients will increase to 65.7 million in 2030 and 150 million in 2050 if there are no effective measures. With the aggravation of aging population in China, the number of AD patients is the largest

in the world and increasing every year. In 2010, the epidemiological survey showed that the incidence of AD in China was 5.69 million, with an annual incidence of 6.25‰; the elder over 55 years old are most likely to have AD [2]. Early stage of the disease can affect the daily life of patients; due to all kinds of factors, it can lead to a variety of complications or organ failure and death later [3].

AD was first proposed by Alzheimer [4] in 1907, a German neuroscientist. He pointed out that AD is an irreversible age-related degenerative disease of the nervous system; the main pathological markers of AD were nerve fiber tangles and senile plaques. In 1998, this finding was confirmed again by the Institute of Neuropathy, University of Munich, Germany. There is a large number of nerve fiber tangles and amyloid plaques, especially in the epithelium of the cerebral cortex of AD patients [5]. At present, the pathogenesis of AD is not completely clear. There are some theories are accepted by the public: the abnormal of cholinergic neurons, β-amyloid protein and its neurotoxicity, hyperphosphorylation of tau protein [6]. However, AD is a complex disease caused by genetic and environmental factors; a single hypothesis cannot fully explain its pathogenesis. Some new hypotheses, such as the hypothesis of inflammation, insulin, oxidative imbalance and gene mutation have brought into sharp focus in recent years [7].

2. The Treatment of AD

At present, among the five drugs approved by FDA (Food and Drug Administration) for AD included cholinesterase inhibitors (donepezil, rivastigmine and galantamine) and N-methyl D-aspartase NMDA receptor antagonist, but these treatments only have modest symptomatic effects for relatively short-time periods, while drugs aimed at affecting the course of disease are still in the preliminary stage of research [8]. Cholinesterase inhibitors and excitatory amino acid receptor antagonists are aimed to improve cognitive disorders of AD; Antipsychotics, antidepressant and Benzodiazepines can effectively treat the psychobehavioral symptoms of AD patients [9]. Aducanumab (BIIB037) is a human recombinant monoclonal antibody targeting a polymerized form of β-amyloid, including soluble oligomers and insoluble fibrils deposited in amyloid plaques in the brains of AD patients. Biogen applied Aducanumab in clinical trials of 166 patients, showed that it could reduce amyloid plaque in patients with precursor or mild AD and slow down the progress of the disease, doses 30 mg/kg were generally well tolerated with no severe or serious adverse events. But its clinical effect still needs to be further studied by promoting the Aducanumab Clinical Project into Phase 3 Trials [10]. Chinese medicine including the active ingredients and compounds have been used in dementia treatment for a long history, such as huperzine A, extracts of ginkgobiloba leaves (EGb), L-3-n-butyiphathlide (L-NBP), TSH (the main water-soluble composition of our traditional Chinese medicine Polygonum multiflorum ThunbIn), ginsenosides, curcumin, *Cornus officinalis*

and so on. Compared with the drugs approved by FDA, there are abundant resources of traditional Chinese medicine in China, It has unique advantages to extract effective, safe and non-toxic single traditional Chinese medicine, active ingredients and compound from natural products, but the effective ingredients of Chinese traditional medicine are complex, so it's partly difficult to extract and separate active ingredients [11]. Because the drug treatment can only delay the course of AD, and some elderly have a high risk of taking drugs, more and more researchers focus on non-drug treatment, some small-scale randomized controlled trials have indicated that non-drug treatments have significant benefits of AD [12]. Noninvasive brain stimulation technology mainly includes transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Studies indicated that TMS can effectively improve the cognitive function of AD patients, especially is the high frequency magnetic stimulation; tDCS can improve AD patients' memory, but it can only stimulate a few brain tissues in the cerebral cortex and subcortex, the stimulation to deep brain tissues is weak, so the symptoms of some patients did not improve significantly [13] [14] [15]. Memory training, cognitive ability training, compensatory cognitive training, motivational interviews and error-free learning are common cognitive training methods. Compared with other non-drug therapies, these therapies are more safe and interesting, and AD patients performed high compliance, but it needs long-term persistence [16]. Study demonstrated that phototherapy can improve the sleep condition of AD patients by adjusting the light intensity and irradiation time, so as to improve their cognitive function [17]. Studies have shown that listening to music and singing can enhance the memory and association ability of AD patients, and have a significant positive effect on the improvement of mood and mental state of their caregivers [18]. For the absence of specific drugs and physiotherapy, the occurrence and development of AD can be effectively delayed by recognizing the potential risk factors of AD and taking early preventive measures.

3. Potential Risk Factors of AD

3.1. Hereditary Risk Factors

Apart from age, the most definite risk factor of AD is family history of dementia. Studies have shown that if there is a first-degree relative suffers from dementia, the risk of one suffers from AD will increase by 10% - 30% [19]. Compared with the general population, someone who has at least two siblings suffers from AD in the family and the risk of AD will increase by 3 times [20]. Studies have shown that race is also an influencing factor of AD. An epidemiological study included 17,639 biological first-degree relatives of 2339 white AD patients and 2281 biological first-degree relatives of 255 African-American AD patients, the cumulative risk of dementia among African-American relatives and white relatives was 43.7% and 26.9% respectively, which showed significant difference ($P < 0.05$) [21].

3.2. Acquired Risk Factors

A variety of polygenic and acquired factors may affect the occurrence of AD, including hypertension, dyslipidemia, cerebrovascular diseases, as well as unhealthy lifestyle, environmental pollution and so on.

3.2.1. Disease

It's estimated that about one third of AD patients worldwide may be attributed to correctable risk factors, such as diabetes, middle-aged hypertension and so on [22]. Among individuals with two or more vascular risk factors in middle ages, the risk of detection of brain amyloid deposition increased to three times in later years, treating vascular risk factors in middle age is considered to be a key strategy to reduce the risk, progression and severity of AD [23]. 1) Hypertension: Multiple cross-sectional studies have shown that middle-aged people with hypertension are more likely to suffer from dementia. Arterial stiffness and blood pressure variability may play an important role in the association between blood pressure and AD [23] [24] [25]; 2) Dyslipidemia: study has shown that high levels of total cholesterol in middle-aged can triple the risk of AD, it might be related to that brain cholesterol can accelerate the formation or deposition of β-amyloid protein [26]; 3) Cerebrovascular diseases: cerebrovascular diseases often coexist with AD, and the complications of AD and vascular diseases are often referred to as mixed dementia. Study has shown that blood flow decreases have been observed before β-amyloid deposition in AD mice model, which directly contributes to amyloid deposition by impairing amyloid clearance [27].

3.2.2. Lifestyle

In recent years, there are enough evidence have indicated that healthy diet and lifelong learning can reduce the risk of cognitive impairment. A meta-analysis of 16 prospective studies found that the overall incidence of dementia and AD decreased by 28% and 45% in individuals with more physical activity than those with less physical activity [28]. Alzheimer's Association and the World Commission on Dementia also suggest that regular physical activity and management of cardiovascular risk factors are associated with reducing the risk of cognitive impairment [29].

3.2.3. Environmental

In a cross-sectional study, 2692 non-smokers aged were enrolled, the results showed that secondhand smoke exposure was associated with increasing the risk of AD [30]. Air pollution and pesticides are also potential risk factors of AD [31] [32].

4. Early Prevention of AD

4.1. Regular Physical Exercise

Long-term regular exercise can delay the occurrence or the progress of AD [33]. Wang Fang [34] found that the spatial learning and memory ability of AD mice

model in the exercise group were significantly higher than that of the other two groups after eight weeks of aerobic treadmill exercise by studying the effect of aerobic treadmill exercise on learning and cognitive ability of AD mice model, aerobic exercise can effectively improve the cognitive function and delay the progress of AD. In a cohort study, 3777 the elderly from 75 communities in southwestern France were randomly selected and followed up every two years for 15 years, the results showed that over the past 15 years, the elderly who were active in exercise and reading were less likely to suffer from dementia than those who did less exercise and reading. More exercise and reading can reduce the risk of dementia by 25% [35]. Wang Yanping's follow-up study also indicated that less exercise could be considered as a risk factor of AD. Taking physical exercises regularly could significantly reduce the risk of mild cognitive impairment turning to AD, which could be considered as a protective factor of AD [36]. A meta-analysis [37] of a series of related studies showed that short-term and medium-intensity aerobic exercise can improve cognitive function and various psycho-behavioral symptoms of AD patients, and then improve the quality of life. Effective way and intensity of exercise can reduce the risk of AD, for mild cognitive impairment patients the symptoms can be improved to a certain extent and the quality of life of AD patients can be improved. Old people should choose the most suitable and safe exercise methods according to their age and physical strength, such as walking, jogging, Tai Chi and general daily activities such as housework, plant flowers and plants, etc.

4.2. Rational Nutritional Diet

Malnutrition and unreasonable diet may accelerate the development of AD and increase the degree of cognitive impairment. Clinical study has shown that advanced AD patients have different degrees of nutritional disorders [38]. Liu Xinyan *et al.* [39] selected 96 AD patients and 100 the healthy and used Spearman correlation analysis and multiple regression analysis to analyze the correlation between nutritional status with AD. The results showed that the worse the nutritional status, the worse the cognitive impairment and the self-care ability of daily life. One study explored the effect of low nutritional status on mild to moderate AD patients, the results showed that low levels of serum total protein and BMI were independently related to AD, which further suggested that low nutritional level involved in the occurrence and development of AD to a certain extent [40]. One study about the correlation between AD biomarkers with BMI index showed that some AD biomarkers such as CSFAb, tau and tauAβ were significantly correlated with BMI. Few overweight and well-nourished people were detected AD biomarkers [41]. Reasonable dietary pattern can also affect the occurrence and development of AD. Some scholars have proposed that the deficiency of various nutrients such as V_{B1}, V_{B12}, folic acid, and metabolic disorders are related to dementia for the impairment of brain tissue and its function [42]. Von Arnim [43] has demonstrated that malnutrition, oxidative stress and homo-

cysteine vitamins play an important role in the pathogenesis of AD. Intaking more saturated fatty acid would increase the risk of AD, fish oil, fish and other unsaturated fatty acids with vegetables can help the regeneration of nerve cell, prevent cognitive decline and the occurrence of AD [44]. In 2013, the Dietary Guidelines for the Prevention of Alzheimer's Disease also recommended avoiding saturated and trans fatty acids, eating more vegetables, increasing the intake of V_E and V_B, eating more mediterranean diets such as fruits and olive oil can reduce the risk of AD. Due to the decline of digestive, absorptive function and basic metabolism of the elderly, the utilization of nutrition in the body is insufficient, while the cognitive ability of AD patients descend. There are different degrees of mental disorders and dysphagia, AD patients are more prone to suffer from malnutrition than other diseases. Improving the nutritional status of patients and maintaining normal nutritional intake in the early stage of disease may be of great significance to improve the mental and behavioral symptoms of AD patients, so that AD patients can benefit from nutritional intervention.

4.3. Social Activities

Frequent mental training activities are of great significance in preventing AD, such as watching TV, playing chess and playing cards can stimulate brain and reduce the risk of AD, while little mental training can increase the probability of suffering from AD. A 26-year longitudinal study of 2513 Japanese-Americans showed that people with the lowest social participation in quartiles had a significantly increased risk of dementia, maintaining certain social ties and participating in social activities could effectively reduce the risk of dementia [45]. Scarmeas *et al.* [46] found that definite social activities can improve the cognitive status of AD patients, which may be related to stimulating brain cell metabolism and giving full play to brain function. The relationship between lifestyle related factors with AD was studied by selecting 238 patients with AD as case group and 476 healthy elderly as control group, family activities, keeping in touch with friends, continuing to work after retirement, tourism and active participation in social activities were included in the study criteria, then multivariate logistic regression analysis was carried out. The results showed that social activities such as playing cards, traveling, reading, exercising and maintaining good relations with family and friends were significantly correlated with AD [47]. Adopting a positive lifestyle and increasing the self-participation of the elderly is conducive to improving the cognitive level of AD patients. Long Yuanxian *et al.* [48] conducted a meta-analysis showed that the combined OR value of a certain amount of social activities was 0.48 [95% CI (0.25, 0.92)], which indicated that the participation of social activities might be beneficial to train the thinking and cognitive abilities of the elderly and be a protective factor of AD. After retirement, the elderly should keep in touch with their family and friends, participate in intellectual social activities frequently, think more, use their brains diligently and train their cognitive thinking ability, which can reduce the incidence of AD in the elderly.

5. Conclusions and Prospects

The pathophysiological process of AD is thought to begin many years before the diagnosis of AD dementia [49]. At present, no effective detection method has been found for early diagnosis and prediction of AD, so most AD patients did not receive regular examination, diagnosis and treatment [50]. The emotional, mental and behavioral symptoms of AD patients during the whole course of the disease have brought tremendous psychological and economic burden to the patients and their families. Identifying potential risk factors and taking early prevention measures, including appropriate sports, reasonable nutritional diet and certain social activities can slow down the occurrence and development of AD. However, systematic and comprehensive prevention guidelines have not yet been formulated. In addition to continuing to study these mechanisms, prevention and treatment of AD by these interventions are also needed. Whether there is gender difference in the improvement effect, whether it can prevent the occurrence of AD and its combined treatment with drugs should be further discussed.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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