Effects of exercise therapy on cognitive function in Alzheimer's disease and mechanisms of action

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Abstract: Alzheimer's disease (AD) is the most common form of dementia, with patients initially experiencing mild memory impairment and then progressive cognitive loss, causing significant stress to families and society. As the number of patients continues to increase, it is important to explore a variety of treatment options. In recent years, non-pharmacological treatments have played a significant role in the prevention and relief of AD. Among them, exercise therapy has become one of the ideal options for non-pharmacological interventions as it can improve cognition and reduce neuropsychiatric symptoms in AD patients. In this paper, the effects and mechanisms of exercise therapy on the cognitive function of AD patients are reviewed in the hope of providing clinical practitioners with some assistance in the treatment and rehabilitation of AD.

Keywords: Exercise therapy; Alzheimer's disease; cognitive function

Alzheimer's disease (AD) is a progressive degenerative disease of the central nervous system and is the most common type of dementia. Patients initially present with mild memory impairment and reduced cognitive function, which gradually progresses to further decline in speech, memory, comprehension and judgement, with almost total loss of cognitive ability in later stages, severely affecting the ability to live independently. Among non-pharmacological treatments, physical exercise [1], multi-sensory stimulation (MSS) therapy [2] and music therapy [3] have been studied to improve patients' cognitive behaviour and psychiatric symptoms, and to improve their quality of life. The present review of the research on exercise therapy in AD is expected to provide some reference for the future application of this therapy in such patients.

1. The development of AD and its pathogenesis

The new diagnostic criteria for AD (NIA-AA criteria) published by the National Institute on Aging in 2011 states that AD can be divided into three stages: preclinical, mild cognitive impairment (MCI) and AD-induced dementia. The neuropathological mechanisms underlying the development of AD continue to be investigated, with some literature suggesting that the pathology of the disease includes depositional lesions, deficient lesions and neurodegeneration, with depositional lesions being the accumulation of neurofibrillary tangles, amyloid plaques, atrophic neurons, neuropil threads and other deposits found in the brain parenchyma. Defective lesions are large areas of atrophy due to loss of nerves, nerve fibre networks and synapses. There are also neurodegenerations containing other factors such as neuroinflammation, oxidative stress and damage to cholinergic neurons [4].

1.1 Senile plaques (SP)

Senile plaques are extracellular deposits of β-amyloid protein (Aβ), which are cleaved by protein hydrolases into amino acid fragments of amyloid precursor protein (APP), eventually forming Aβ40 and Aβ42. Aβ monomers and insoluble amyloid protofibrils can accumulate to form amyloid plaques and spread throughout the brain [5].

1.2 Neurogenic fibrillary tangles (NFTs)

NFTs are abnormal filaments of hyperphosphorylated tau proteins that intertwine to form knotted helical filaments (PHFs) and accumulate in the perinuclear cytoplasm, axons and dendrites, leading to loss of cytoskeletal microtubules and microtubulin-associated proteins. Hyperphosphorylated Tau

proteins are a major component of NFTs in the brains of AD patients [6].

1.3 Synaptic loss in the early stages of AD

synaptic damage in the cortical and limbic systems leads to memory impairment by mechanisms involving defective axonal transport, mitochondrial damage, and oxidative stress, such as the accumulation of Aβ and tau at synaptic sites, processes that ultimately lead to dystrophy and loss of function in dendritic spines, presynaptic terminals and axons [7].

2. Exercise therapy and Alzheimer's disease.

Exercise therapy can be divided into cognitive exercise, physical exercise and integrated exercise. Cognitive exercise includes cognitive stimulation and cognitive rehabilitation; physical exercise refers to aerobic exercise or resistance exercise, etc.; integrated exercise refers to the combination of cognitive exercise and physical exercise according to the patient's actual condition, with a view to achieving better therapeutic interventions.

2.1 Cognitive exercise

Cognitive exercise mainly includes cognitive training (CT), cognitive stimulation (CS) and cognitive rehabilitation (CR). CS is a more hands-on, non-standardised activity that aims to improve overall everyday behavioural functions such as spelling, language and spatial functions [8]. In a study by Fa Wei-Ling and Chen Li, Alzheimer's patients were given regular care combined with the interactive physical games "Gopher" and "Memory Match" for 10 min each time, once a day, and after 18 months, The results showed that the experimental group showed an improvement in cognitive function [9]. The results of the processing of EEG complexity and approximate entropy in patients with mild to moderate cognitive impairment, after 10 days of focused memory impairment training, by Anton Man and Li Yao et al. showed that the memory trainer was of significant value in the establishment of recovery of neural networks in the brain, and the longer the training time, the better the effect.

2.2 Physical exercise

Aerobic exercise [9-10] and resistance training [11] in physical exercise are associated with a reduced risk of cognitive decline. Aerobic exercise benefits primarily by improving brain function, and animal experiments by Cotman and colleagues in 1995 demonstrated that exercise increased brain-derived neurotrophic factor (BDNF) in the hippocampus and cortex, thereby promoting neuronal function [12]. Lv Huanyu and Shang Ziqi [13] also found that aerobic exercise can upregulate positive BDNF expression, and at the same time, increase the level of the anti-apoptotic factor B lymphocytoma and decrease the level of related pro-apoptotic factors, thus achieving effective inhibition of neuronal apoptosis, so it is expected that exercise can regulate BDNF expression to treat Alzheimer's disease and other diseases related to cognitive function.

Resistance exercise refers to exercises in which the main focus is on counteracting strength, There is a positive causal relationship between muscle adaptations during resistance exercise and brain function in people with mild cognitive impairment[14]. An experiment by Liu-Ambrose et al. conducted different frequencies of resistance exercise to study the effects on step frequency, Resistance exercise twice a week for 6 months not only significantly improves memory capacity but also results in positive changes in memory area haemodynamics. There are data showing changes in the haemodynamics of the anterior left middle temporal gyrus and the left anterior insula extending to the extra-orbital cortex after up to 12 months of twice-weekly resistance exercise, but not during weekly exercise [15].

2.3 Integrated exercise

Cognitive function can be reinforced by learning new things, so cognitive training should be based on information processing and on top of this integrated reinforcement, combining and training the same type of exercise in different ways as a way to deepen the patient's impressions [16] and thus improve cognitive function. A study by Yuming Chen et al. confirmed that exercise can improve executive performance in patients with mild cognitive impairment [17]. Repetitive physical cognitive exercise is effective in improving overall cognition (e.g. working memory, situational memory and executive ability) and enhancing frontal lobe cognitive function and neuroplasticity [18]. Combined exercise therapy has

shown more advantageous results in improving cognitive function and enhancing executive performance compared to single training groups [19].

3. Potential mechanisms of exercise therapy to improve cognitive function in AD patients

Exercise interventions do benefit cognitive function, but the underlying molecular mechanisms have been theorized, with the more established mechanism being extracellular β-amyloid (Aβ) deposition, dominated by Aβ40 and Aβ42 proteins, Aβ monomers and insoluble amyloidogenic fibrils, which can accumulate to form amyloid plaques and spread throughout the brain. Chen Ke [20] et al. showed that exercise can activate silent mating-type information regulation 2 homolog 1 (SIRT1), whose acetylation inhibits secretase activity and reduces Aβ production and hyperphosphorylated Tau protein aggregation; Zhang Yeting [21] suggested that long-term aerobic exercise could increase the methylation rate of Notch1 and Hes1 and the expression of Ngn2 by regulating the hippocampal Notch1 signaling pathway in AD mice, which might enhance neuronal proliferation and migration differentiation during adult hippocampal neurogenesis (AHN) in AD mice and reduce the occurrence of neuronal apoptosis.

As the central nervous system is sensitive to oxidative stress, exercise-induced reactive oxygen species (ROS) play an important role in regulating cognitive function and improving neural remodelling. Exercise inhibited obesity-induced ROS production and Tau protein hyperphosphorylation, significantly altering brain tissue pathology and effectively preventing learning and memory impairment compared to the quiet group. In a study by Sun Ruifeng and Gong Weijun [22], it was mentioned that exercise intervention strategies could increase the bioavailability of neurotrophic factors such as BDNF, insulin-like growth factor -1 (IGF-1) and vascular endothelial growth factor (VEGF) by increasing the bioavailability of these factors, which in turn could increase the bioavailability of these factors. (IGF-1) and vascular endothelial growth factor (VEGF), which in turn regulate exercise-induced synaptic plasticity and enhance cognitive function [23]. Aerobic exercise leads to positive expression of BDNF [24], BDNF secretion is involved in the Conditioned Taste Aversion (CTA) memory fading process via the Erk signalling pathway, and BDNF in the insula intervenes in memory fading by inhibiting neuronal apoptosis, BDNF is extremely important in synapses, neuroplasticity and the development of learning and memory. The exercise-derived muscle factor irisin regulates synapses by activating BNDF expression and inhibiting the Aβ/NF-κB pathway, which in turn promotes neurogenesis and synaptic germination in the hippocampus, enhances synaptic transmission efficiency, reduces neuronal apoptosis and improves cognitive performance [25]. Autonomic exercise upregulates skeletal muscle and serum irisin levels by upregulating the synthesis of skeletal muscle peroxisome value-added substance-activated receptor-1a (PGC-1α), which in turn promotes irisin FNDC5 gene and protein expression, and upregulates skeletal muscle and serum irisin (irisin), which crosses the blood-brain barrier to produce neuromodulation. irisin also prevents Aβ binding to nerve cells and inhibits NF The expression of pro-inflammatory factors such as TNF-α, IL-1β and IL-6 downstream of the κB signalling pathway reduces neurotoxicity, thereby protecting the cognitive abilities of the AD brain [26]. proteasome activity in brain regions of AD patients is significantly reduced compared to normal organism performance, and in causing the accumulation of ubiquitinated proteins in the organism also exacerbates the inhibition of 26S protease function, resulting in increased Aβ deposition The increase in Aβ deposition. In contrast, the expression of proteasome and its subunit PSMB5 in the hippocampus of AD mice was enhanced after intensive training compared to that of AD model mice, suggesting that intensive training may improve cognitive dysfunction by modulating hippocampal proteasome activity and reducing Aβ deposition in AD mice [27]. Among them, long-term adherence to moderate intensity aerobic exercise can improve and repair the Alzheimer's disease brain environment and brain area function, improve brain energy metabolic function, reduce the production of inflammatory factors, neurotoxic proteins, oxidative stressors, contribute to neuronal cell plasticity and neuronal signaling, and finally treat and delay Alzheimer's disease.

4. Conclusion and outlook

Overall, exercise therapy is a non-pharmacological, low-cost, low-side effect intervention that has advantages in improving cognitive function, relieving neuropsychiatric symptoms and improving the quality of life of patients. Exercise therapy has a protective effect on the cognition of AD patients, especially on autobiographical and situational memory, psychomotor, executive and overall cognitive abilities. Especially for patients in the pre-clinical phase, i.e. not yet suitable for pharmacological treatment, exercise therapy has more obvious advantages and is therefore recommended to intervene in

such patients with a view to intervening in the course of their dementia. However, in patients with moderate to moderate AD, exercise interventions should only be used as an adjunct to Alzheimer's disease, and patients should continue to take their medication regularly during the intervention period. Furthermore, as high-quality experimental studies are prospective, randomised and blinded, there is a need to provide more uniform and rigorous methodological studies and clinical trials to add more evidence to support that exercise therapy can slow the progression of AD. The multifaceted combination of exercise and dance, art and multi-sensory approaches to non-pharmacological treatment has also had impressive results and is a popular area of research at this stage. Individualised intervention programmes should be developed for each patient.

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