

Advancements in Non-Pharmacological Interventions for Mild Cognitive Impairment Induced by Alzheimer's Disease

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Abstract: Mild cognitive impairment (MCI) associated with Alzheimer's disease (AD) represents the initial clinical manifestation of AD. Early clinical intervention for MCI is crucial for delaying or potentially reversing the progression of AD. Given the increasing prevalence of population aging, AD, as the leading cause of dementia, has imposed significant social and familial burdens. Therefore, early identification, diagnosis, and intervention of AD are of paramount importance both clinically and socially. This review aims to summarize recent advancements in the clinical diagnosis and non-pharmacological treatment of MCI derived from AD, thereby enhancing understanding of this condition, providing valuable references for clinical practice, and ultimately improving patients' cognitive function and quality of life.

Keywords: Alzheimer's disease; Mild cognitive impairment; Non-drug therapy

1. Introduction

Mild cognitive impairment (MCI) associated with Alzheimer's disease (AD) denotes a pre-dementia stage characterized primarily by subtle cognitive deficits that align with the pathophysiological features of AD [1]. MCI serves as an intermediary phase between normal aging and dementia [2], presenting a significant risk for progression to AD [3]. Addressing AD-related MCI has emerged as a critical opportunity for preventing or potentially reversing AD. Considering the pathogenesis, pathological mechanisms, and clinical manifestations of AD-related MCI, the 2021 Chinese Expert Consensus on the Diagnosis and Treatment of Alzheimer's Disease-associated Mild Cognitive Impairment advocates a holistic treatment approach that integrates pharmacological and non-pharmacological interventions[4]. This review synthesizes and evaluates the latest domestic and international research on AD and MCI treatments, focusing on the benefits and limitations of non-pharmacological therapies for AD-related MCI.

2. Clinical Characteristics and Diagnostic Criteria of Amnesic Mild Cognitive Impairment (aMCI) Derived from Alzheimer's Disease

The clinical characteristics of Alzheimer's disease (AD)-related mild cognitive impairment (MCI) are as follows: (a) Mild cognitive impairment, characterized by recent memory loss and a decline in the ability to acquire new knowledge, may also involve dysfunction in other cognitive domains[5]; (b) primarily minor impairment of social function without a significant decline in basic activities of daily living[6]; (c) various non-cognitive neuropsychiatric symptoms can manifest in the early stages[7]. Currently, there are no universally accepted diagnostic criteria for AD-related MCI. However, combining the diagnostic criteria initially proposed by the National Institute on Aging-Alzheimer's Association (NIA-AA) working group in 2011 with the consensus criteria established by experts in the diagnosis and treatment of AD-related MCI in 2021, the diagnostic criteria exhibit the following features: 1. MCI consistent with the aforementioned clinical characteristics as assessed by relevant scales; 2. biomarker profiles and imaging findings consistent with AD-specific characteristics.

3. Non-drug therapy

With the deepening understanding of the pathophysiology of Alzheimer's Disease (AD), its treatment has transitioned from single-target pharmacotherapy to a more comprehensive and multidisciplinary approach. As an essential component in addressing AD-induced Mild Cognitive Impairment (MCI), non-pharmacological therapies are currently categorized into three primary clinical modalities: lifestyle modifications, cognitive interventions, and brain stimulation therapies.

3.1 Lifestyle intervention

3.1.1 Exercise therapy

Exercise therapy has demonstrated significant improvements in cognitive performance among older adults. Research

indicates that resistance training not only enhances cognitive function and memory in elderly individuals and Alzheimer's disease (AD) patients but also modulates neuroinflammatory responses and reduces A β burden through neuroprotective mechanisms[8]. Animal studies have revealed that resistance training can mitigate amyloid load, tau pathology, and neuroinflammation, thereby improving cognitive function in AD mice[9]. A Canadian clinical trial further showed that a multi-domain intervention combining progressive aerobic resistance exercise with sequential cognitive training significantly improved overall cognition in elderly individuals with mild cognitive impairment (MCI), including memory, attention, word recognition, and orientation. The multi-domain approach yielded superior results compared to exercise alone[10]. Additionally, studies have highlighted the benefits of integrating resistance training with aerobic exercise for enhancing memory and cognitive function while minimizing AD pathophysiology[11].

3.1.2 Dietary therapy

Numerous studies have demonstrated that among various dietary patterns, the Mediterranean diet (MeDi) is effective in reducing mild cognitive impairment (MCI) and its progression to dementia[12]. Bioactive compounds in MeDi, such as phenolic compounds, have been shown to mitigate neuroinflammation through their antioxidant properties[13]. Adherence to MeDi has been associated with a reduced rate of cognitive decline in patients with Alzheimer's disease (AD), while also enhancing overall cognition, episodic memory, and lowering the risk of cognitive impairment and neurodegenerative diseases[14]. A systematic review of small sample studies suggests that the ketogenic diet may similarly improve cognitive performance in early-stage AD or MCI[15]. Additionally, research indicates that probiotics can enhance cognition and alleviate gastrointestinal symptoms in patients with AD, MCI, and Parkinson's disease (PD) by reducing inflammatory responses and improving lipid metabolism[16].

3.1.3 Improve sleep

Approximately 60% of Alzheimer's disease (AD) patients experience sleep disorders during the preclinical stage[17]. A study demonstrated that insomnia, sleep apnea, and other sleep-related issues, such as sleep fragmentation and movement disorders during sleep, are associated with an increased risk of developing AD. In contrast, daytime napping or excessive daytime sleepiness only exhibited a higher risk of AD development[18]. Sleep represents a modifiable and treatable risk factor for AD. Evidence suggests that improving sleep quality can enhance cognitive function in individuals with mild cognitive impairment (MCI) or AD. Additionally, a limited number of studies have indicated that continuous positive airway pressure (CPAP) therapy, as an effective treatment for obstructive sleep apnea, may slow cognitive decline in elderly individuals with MCI or AD who also suffer from this condition[19].

3.2 Cognitive intervention

As a non-pharmacological treatment to enhance cognition, cognitive intervention encompasses various approaches, with restorative cognitive training being the most widely adopted method currently[20]. Memory impairment is the most prominent feature of Alzheimer's disease (AD)-related mild cognitive impairment (MCI). Cognitive intervention enhances resilience to neurodegenerative diseases by augmenting cognitive reserve[21]. Furthermore, studies based on magnetic resonance imaging (MRI) have demonstrated that cognitive training can alter the resting state of the brain by improving cerebral blood flow, brain network connectivity, and white matter integrity in healthy elderly individuals. This suggests that cognitive training can enhance cognitive function in older adults through the promotion of neuroplasticity[22]. Presently, cognitive training not only relies on traditional face-to-face modes but also leverages computer-based platforms. Due to its ability to integrate technical functionalities more effectively, computerized cognitive training (CCT) enriches the training modalities and enhances user experience, making it more prevalent in clinical settings. Relevant studies indicate that CCT significantly improves verbal episodic memory, visual episodic memory, and working memory, suggesting its potential to enhance memory function in MCI patients[23]. In another analysis examining the "Ecological impact of VR-based cognitive training on Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) in MCI and AD patients," findings revealed that VR-based cognitive training significantly improved IADL in both MCI and AD patients, with MCI patients benefiting more than those with AD[24]. However, there remains a paucity of clinical studies on cognitive training, and some evidence suggests that MCI patients may not derive significant benefits from such interventions. Consequently, the development of standardized, intelligent, and multi-modal CCT represents one of the future directions for non-pharmacological treatments targeting AD-related MCI.

3.3 Brain stimulation therapy

Brain stimulation therapy encompasses both traditional acupuncture and repetitive transcranial magnetic stimulation (rTMS). Acupuncture, an essential component of traditional medicine, has demonstrated significant efficacy in treating

various diseases. A randomized clinical trial revealed that acupuncture can enhance cognitive function in patients with mild cognitive impairment (MCI), with a 30-minute needle retention time proving more effective than 20 minutes[25]. rTMS is a non-invasive brain stimulation technique at the forefront of innovative and safe pilot therapies for improving cognitive function in older adults[26]. Animal studies have shown that rTMS at two different frequencies significantly improves learning and memory in mice, with high-frequency rTMS yielding better results than low-frequency treatment. Additionally, research indicates that low/high frequency rTMS applied to the left/right or bilateral dorsolateral prefrontal cortex (DLPFC) may positively impact cognitive functions (such as executive, memory, language, and visuospatial abilities) and behavioral abnormalities (such as apathy) in MCI patients[27].

4. Summary and prospect

As a critical phase characterized by the initial clinical symptoms of Alzheimer's Disease (AD), AD-related Mild Cognitive Impairment (MCI) exhibits complex pathophysiological features. However, its underlying pathogenesis and pathological characteristics remain poorly understood. Given the current lack of effective therapeutic approaches for AD, managing AD-related MCI has emerged as a crucial window for preventing and intervening in AD progression. Presently, the treatment of AD-related MCI is in an exploratory clinical stage, with combined interventions becoming a novel focus. Although preliminary studies indicate that pharmacological treatments can enhance cognitive function and delay the progression from AD-related MCI to AD, there remains a paucity of large-scale, long-term clinical trials to fully evaluate the efficacy, safety, and sustainability of these drugs. Non-pharmacological therapies, which are integral to the management of AD-related MCI, have demonstrated potential in improving cognitive function and quality of life, attracting increasing clinical attention. Nonetheless, the absence of standardized protocols for these interventions limits their application, as they often require significant cooperation from medical staff, patients, and their families. Future research should explore the mechanisms and long-term efficacy of combined interventions, which represent a promising new direction in the treatment of AD-related MCI.

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