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Research Status of Mild Cognitive Impairment Complicated with Depression

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Abstract

Mild cognitive impairment is a transitional state of cognitive impairment between normal aging and dementia. As the most common complication of mild cognitive impairment (MCI), depression seriously affects the physical and mental health of middle-aged and elderly people when co-morbid with MCI, and it is also an important risk factor for the development of dementia in mild cognitive impairment (MCI). However, the pathogenesis of depression in patients with mild cognitive impairment is still unclear, and the related treatment options are still controversial. In this paper, we reviewed recent domestic and international studies to summarize the epidemiological features, pathogenesis, and treatment methods of depression in patients with mild cognitive impairment, to provide a reference for clinical treatment of this disease and to provide an outlook on future research directions.

Keywords

Mild Cognitive Impairment; Depression; Pathogenesis.

1. Introduction

With the progress of population aging, dementia has become the third leading cause of serious threat to human life and health after cardiovascular diseases and malignant tumors. Dementia not only affects the quality of life of the elderly, but also imposes a heavy economic burden on families and society. Mild cognitive impairment (MCI) is a progressive decline in memory or other cognitive functions that does not affect the ability to perform daily living activities and does not meet the diagnostic criteria for dementia [1], MCI is considered to be a transitional stage between normal aging and Alzheimer disease (AD), and there is a trend toward AD. The clinical manifestations of MCI include diminished memory, language function, attention, executive function, visuospatial structure function, or computational power, with memory loss being the most dominant and common clinical manifestation, with recent memory loss being evident. Depression is the most common psychobehavioral symptom in patients with mild cognitive impairment, and follow-up studies have found that psychobehavioral symptoms are a risk factor for conversion of MCI to dementia, and even mild psychobehavioral symptoms increase the risk of conversion of MCI to dementia or AD. pathophysiological changes in AD patients are difficult to reverse, patients have severe cognitive impairment, and there are no ideal medications and therapies that can delay and improve the condition of AD. There are no ideal drugs and therapies to delay and improve AD [2]. It has been found that MCI patients retain some cognitive ability and cognitive plasticity and are at the best time to implement interventions and prevent dementia [3, 4]. Therefore, it is particularly important to identify early interventions for patients at risk of mild cognitive impairment combined with depression to improve cognitive decline and delay their transition to dementia.

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2. Epidemiological Features

2.1. Incidence of MCI

Patients with MCI are at high risk of dementia, and follow-up studies on MCI have shown that approximately 10% to 30% of patients progress to dementia within 1 year [5] and 20% to 66% within 2 to 4 years [6]. Due to the different diagnostic criteria for MCI, the prevalence of MCI in the population varies considerably in different studies, with a prevalence of 10% to 20% in people aged 65 years and older in population-based studies [7]; other studies have confirmed that the prevalence of MCI increases significantly with increasing cohort age, with MCI prevalence in people aged 60-64 years at 6.7%; 65-69 years 8.4% in the cohort; 70-74 years, 10.1%; 75-79 years, 14.8%; and 25.2% in the 80-84 years age group[8]. A domestic study on the prevalence of MCI in China from 2001 to 2015 showed that the prevalence of MCI in the community population aged 55 years and above in China was 14.5% [9]. The results of another study on the prevalence of MCI in the elderly in China showed that the prevalence of MCI in the elderly in China was 14%, including 12.1% in men, including 12.1% in men; the prevalence increased significantly with age, with 8% in the 60-69 age group, 13.1% in the 70-79 age group and 23.4% in the 80+ age group [10], which is similar to the results of foreign studies. The above data indicate a high prevalence of MCI at home and abroad and a close correlation with age, a problem that is becoming increasingly serious with the progress of population ageing in China.

2.2. Prevalence of Comorbid Depression among MCI Patients

Patients with MCI suffer from generalised psychiatric behavioural disorders, mainly apathy, depression, anxiety and nocturnal behavioural disorders. The results of a population-based study abroad suggest that MCI patients are more likely to have generalised depression and anxiety disorders than the normal population [11]. The prevalence of depression in a clinical sample was 40%, which may be higher in practice[12]. Shi Yahang et al. found a 31.82% prevalence of depression in 154 community-based MCI patients [13], and Zhao Yu et al. investigated 241 MCI patients, of whom a total of 71 had comorbid depressive symptoms, with an incidence of 29.46%, 83.10% with moderate depression and 16.90% with major depression [14]. Other follow-up studies and cross-sectional studies have shown that depression is a risk factor for MCI and that depressive symptoms may precede MCI [15]. In conclusion, depressive symptoms are an independent risk factor for the progression of MCI to dementia and their impact should not be underestimated.

3. Pathogenesis

At present, the pathogenesis of depression associated with MCI has not been fully understood by modern medicine, and most scholars believe that it is the result of a combination of endogenous molecular biological factors and psychosocial factors. First, MCI co-morbid depression is closely related to neurobiological changes. Autopsy findings have revealed similar pathological features in MCI patients and most AD, namely (i) extracellular aggregation of age spots composed of β-amyloid β-protein (Aβ) and (ii) intra-neuronal aggregation of neurofibrillary tangles composed of hyperphosphorylated tau protein. These pathological markers are positively associated with neuronal degeneration, neuroinflammation, microglia activation, blood-brain barrier dysfunction and cognitive decline. Hippocampal atrophy is an important link between MCI and depressive symptoms, and related studies have revealed varying degrees of atrophy in the anterior hippocampus, internal olfactory cortex, sphenoid gyrus and amygdala in MCI patients on imaging [16]. The hippocampus is the main mediator of emotional responses in the brain [17] and is associated with situational memory. This region has a high density of glucocorticoid receptors, and studies in depressed patients have found that depression-induced stress leads to increased cortisol secretion in the blood, an alteration

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that in turn acts on glucocorticoid receptors in the hippocampus, leading to neurotoxicity and impairment of hippocampal function leading to cognitive impairment [18]. Secondly, the underlying mechanism of MCI co-occurring depression may be related to the production of immune inflammation within the brain. Ageing increases peripheral immune responses and disrupts immune signalling within the brain, leading to excessive activation and initiation of microglia, increased production of the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α, and reduced production of anti-inflammatory molecules. The continued activation of microglia leads to inefficient clearance of neurotoxic molecules by the brain and neuronal loss resulting in neurological impairment; cytokine production increases oxidative stress within neuronal cells and damages glial cells in the prefrontal cortex and amygdala of the brain, and damage to this region is a direct cause of depression [19]. Some studies have found that inflammatory changes in the brain are closely associated with the development of depression, and that inflammation may cause immune cells and their cellular targets to become resistant to glucocorticoids, disrupting glucocorticoid receptor function and increasing the inflammatory response, further exacerbating depressive symptoms. David et al. also demonstrated that elevated levels of peripheral inflammatory markers in the brain are associated with the severity of depression and cognitive symptoms of depression [20]. In addition, patients with MCI are at higher risk of depression due to the psychological stress associated with neurological deficits, changes in social status and interpersonal relationships, as well as the fact that patients with more rapid disease progression are less likely to adapt to the problems associated with the disease in the short term.

4. Therapeutic Measures

4.1. Pharmacological Treatment

For patients with MCI co-morbid with depression, no clear-cut effective medication has been identified to improve cognitive impairment and there is no uniform prevention and treatment protocol. A series of randomised, placebo-controlled Meta-analyses have reported poor drug efficacy in patients with MCI co-morbid with depression, and a large number of randomised, double-blind, placebo-controlled trials on drug efficacy are lacking. Current treatment principles focus on identifying and controlling risk factors for primary prevention and symptomatic treatment for secondary prevention. A 3-4 year randomised, double-blind, placebo-controlled study by Steven et al [21] of the cholinesterase inhibitor cabalactam showed that cabalactam reduced the incidence of AD in women with wt/wt genotype compared to placebo. The results of studies with other cholinesterase inhibitors such as donepezil and galantamine have shown that these drugs do not reduce the rate of conversion from MCI to AD and have greater adverse effects. Another study found that the ionotropic glutamate receptor blocker memantine was neuroprotective by inhibiting oxidative stress, reducing the release of pro-inflammatory factors and improving SPECT perfusion in the right inferior temporal region [22]. Gavrilova [23] found that EGb 761 could improve mitochondrial function, promote neural plasticity and slow down cognitive impairment in patients. This study also showed that EGb 761 had significant therapeutic effects on mental and behavioral symptoms such as anxiety and depression. The current study of brain cell metabolic activators such as oxiracetam has confirmed that this drug has certain curative effect on reducing the plasma neuron-specific enolase (NSE) level, increasing the energy storage in the brain, improving ATP conversion, and improving the tolerance of brain tissue to hypoxia to improve cognitive dysfunction, but it has no significant improvement in patients with depression [24] . For MCI patients with depression, antidepressants are often used in clinical intervention, mainly including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and 5 - hydroxytryptamine-noradrenaline reuptake inhibitors (SNRIs). Matthias [25] recently found that SSRIs can

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significantly improve the decline of cognitive function in patients with depression. At the same time, imaging results showed that SSRIs also reduced the gray matter atrophy of frontal and temporal cortex in patients, but it is worth noting that the treatment of MCI patients with depression by traditional antidepressants remains controversial.

4.2. Rehabilitation Treatment

At present, cognitive function training, physical exercise, computer cognitive training, lifestyle intervention and other methods can be used for non-drug treatment of MCI complicated with depression. A large number of clinical studies and randomized controlled trials have shown that behavioral intervention, especially aerobic exercise and psychological intervention therapy, is an effective intervention for cognitive function and improvement of depressive symptoms in patients with MCI complicated with depression. Zhao et al. studied the effect of square dance on the cognitive function and depression level of elderly MCI patients with depressive symptoms. The results showed that after three months of intervention, the total score of Montreal Cognitive Assessment Scale-Particulation (MoCA-P), visual spatial executive function and delayed memory in the intervention group were significantly higher than those in the control group ($P < 0.05$), and the depression level was significantly lower than that in the control group ($P < 0.05$), suggesting that square dance could improve the cognitive function of elderly MCI patients, especially memory and executive function, and significantly improve the depressive symptoms of patients. It may delay the transformation of MCI to dementia [26]. A meta-analysis of randomized trials of computerized cognitive training (CCBT) in patients with MCI suggests that [27] computerized cognitive training is effective for patients ' overall cognition, memory, working memory and attention, and helps to improve psychosocial functions, including depressive symptoms. Recent research results also confirmed that the self-rating anxiety scale (SAS) scores of patients before and after CCBT intervention were lower than those before intervention ($P < 0.01$), and the scores of the experimental group were significantly lower than those of the control group ($P < 0.01$). One month after intervention, the SAS scores of the two groups were higher than those after intervention, and the scores of the experimental group were lower than those of the control group ($P < 0.01$). The SDS scores of the two groups after intervention were lower than those before intervention ($P < 0.01$) [28]. This result suggests that CCBT may be a powerful treatment for MCI patients with depression and preclinical AD. Gretchen [29] highlighted the role of mindfulness and cognitive training in improving cognition and emotion in patients with mild cognitive impairment. Preliminary evidence suggests that cognitive training has a positive effect on cognitive function (attention, psychomotor function, memory, executive function), depression and anxiety in patients with MCI complicated with depression. Among all the above non-drug treatments, the evidence level of cognitive function training and CCBT is relatively high. In the further treatment study, drug treatment, cognitive function training and CCBT were combined through large longitudinal randomized controlled trials to explore the reliable scheme of early intervention for MCI patients with depression.

4.3. Acupuncture Therapy

Acupuncture treatment has the advantages of easy operation and precise efficacy. The treatment of depression complicated by MCI is often based on the Du meridian, Gall Bladder meridian, Bladder meridian, Pericardium meridian and Liver meridian. Zhang Dongliang [30] randomly divided 70 post-stroke MCI patients into two groups of 35 each. The observation group was treated with acupuncture to relieve depression and the control group was treated with oral donepezil hydrochloride. Wang Yan et al [31] randomly divided 60 patients with MCI complicated by depression into 2 groups of 30 each. The patients in the control group were given conventional treatment and conventional cognitive function rehabilitation training, while the patients in the study group were treated with Tongdu Waking Shen Acupuncture Method

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on top of the control group. The study group had higher scores on the Neuropsychiatric Questionnaire (NPI-1 and NPI-2) and higher scores on the Ability to Perform Daily Living (ADL) than the control group ($p<0.05$).

5. Summary and Prospects

Previous studies have found that depressive symptoms are a common complication of MCI, and with an ageing population, the incidence of MCI has increased significantly. The presence of depressive symptoms seriously affects the quality of life of MCI patients, exacerbates the progression of MCI, and places a heavy burden on their families and society. At present, there is no effective way to reverse the progression of MCI with depression, and pharmacological treatment mostly emphasises symptomatic treatment and early prevention, with poor long-term outcomes. However, there are also certain problems, such as poor reproducibility, varying evaluation criteria, uneven skills of practitioners, and the application of Chinese medicine alone may be slow to take effect and fail to achieve the desired results in a short period of time, making it difficult for some patients to adhere to the treatment. Therefore, in order to solve these problems and improve the quality of survival of patients, large-scale and standardised clinical studies are needed in the future to explore new options for the treatment of this disease, in order to reduce the suffering of patients and improve their quality of survival.

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