Review

Variable risk factors affecting the development of mild cognitive impairment（MCI）in the elderly

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Abstract

MCI is considered to be a transitional state in which cognitive function gradually deteriorates from normal to dementia and it is characterized by a decline in several cognitive areas such as executive function, memory, language, processing speed, or attention. At present, the clinical treatment effect of dementia is not ideal, so we will shift the focus of research to MCI, to find the modifiable risk factors, potential mechanisms and effective preventive measures of MCI occurrence in the elderly. And decrease the incidence of dementia and the health or economic burden on families and society. We now find that the variable risk factors affecting the occurrence and development of MCI in the elderly include vascular risk factors, pulmonary health, educational and psychiatric factors. We mainly review the effects of these modifiable risk factors on cognitive function, the potential mechanism of action, and propose intervention measures to improve cognitive function.

Key words: mild cognitive impairment, Dementia, Risk factors, intervention

Introduction

MCI is considered to be a transitional stage between normal cognition and dementia and a precursor to Alzheimer's disease (AD). It is characterized by impaired subjective memory and moderate deficits in at least one area of cognition, such as executive function, memory, language, processing speed, or attention [1].The transition from normal cognition to MCI and then to AD is a continuous process of the occurrence and development of cognitive disorders, so patients with MCI are considered to be at high risk of AD [2].In contrast to MCI, AD can affect multiple cognitive domains and materially interfere with daily activities, while MCI may affect only one cognitive domain and not materially interfere with daily activities [3]. In China, 15.2%-15.9% of the elderly over 60 years old suffer from MCI, and the annual incidence of MCI is about 6.36% [4], The average annual conversion rate from MCI to AD was 18.4% [5].The neurobiological features of MCI are hypoperfusion and hypometabolism in the temporoparietal cortex, atrophy of the medial temporal lobe, especially in the nasal cortex, increased tau and phosphorylated tau and decreased Aβ42 in the cerebrospinal fluid, and Aβ42 deposition in the brain [6].The World Dementia Report 2018 estimated that 46.8 million people were living with dementia globally in 2015, a number that is expected to triple by 2050.[7] Cognitive impairment has caused serious economic burden to individuals, families and society, but the treatment of AD patients is still not ideal. MCI as a precursor of AD has become a new direction of research. A variety of risk factors can affect the occurrence and transformation of MCI. Therefore, this review mainly lists the influencing factors of MCI, which can help early detection and intervention of risk factors, reduce the incidence of MCI and block its transformation to AD.

Variable risk factors

T2DM

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia caused by multiple etiologies, which can cause chronic progressive lesions of multiple organs and systems. It is estimated that 537 million people already suffered from diabetes in 2021, and this number is expected to reach 643 million by 2030 and 783 million by 2045 [8]. That means one in 10 people worldwide will have diabetes in the next 20 years, and more than 90 percent of them will have T2DM. Studies have shown that [9] T1DM and T2DM can increase the incidence of cognitive impairment, and T1DM increases the risk of dementia much more than T2DM.

However, as the number of elderly patients with T1DM is much lower than that of elderly patients with T2DM, the research on the relationship between T1DM and MCI is far less than that between T2DM and MCI. We therefore review the risk of MCI in T2DM and its impact on the progression of MCI to dementia.

It has been established that T2DM is one of the modifiable risk factors for MCI[4, 9, 10].In the follow-up of diabetic patients for more than 10 years, it was found [10],hat the average prevalence of MCI in the diabetic group was 30.66 ± 3.09%, significantly higher than the 22.32 ± 2.75% in the non-diabetic group, which was close to the results reported in 2015 that 25-36% of diabetic patients had MCI[11]. A few scholars believe that although diabetes increases the prevalence rate of MCI, it does not seem to affect its progress [10, 12]； However, most scholars believe [13, 14]that the presence of diabetes may increase the risk of MCI transforming into dementia at any stage. There are obvious differences between the two conclusions, which may be related to the sample size, age of participants, follow-up time and other reasons, which need to be further studied and followed up. When T2DM is combined with other diseases, the incidence of MCI may be higher than that of T2DM alone. Ryuno[15] found in a 3-year follow-up study that diabetes combined with hypertension may have a greater impact on future cognitive decline than diabetes alone, and the two may have a synergistic effect. In addition, the longer duration of diabetes, retinopathy, high cholesterol level, occurrence of stroke events and cardiovascular disease in patients with diabetes may increase the occurrence of MCI. Currently, it has been found that the use of statins may reduce the chance of cognitive dysfunction in patients to some extent [12-14, 16].

T2DM may cause MCI for a variety of reasons: cerebrovascular disease is the main cause. Diabetes can cause vascular brain injury, cerebral hypopfusion ,white matter disease, and eventually MCI or dementia [12, 17]. Secondly, galactolectin 3 (Gal3) plays an important role in the progression of cognitive impairment in diabetes, and the elevated level of Gal3 in blood circulation may be related to the development of MCI in patients with type 2 diabetes [18]. The third is inflammatory response. The levels of some inflammatory markers, such as serum soluble vascular adhesion molecule (svcAM-1) and highly sensitive C-reactive protein (Hs-CRP), are significantly positively correlated with MCI in type 2 diabetes mellitus, which may be involved in the pathogenesis of MCI [19]. Fourth, patients with MCI in type 2 diabetes showed significantly reduced amplitude of low-frequency fluctuation (ALFF) in various brain regions significantly related to cognitive ability, such as bilateral insula, left middle frontal gyrus and left precuneus, and significantly increased ALFF in temporal gyrus

and fusiform gyrus [20]. In addition, chronic hyperglycemia, severe hypoglycemia, hyperinsulinemia, disturbed insulin homeostasis in brain, advanced glycation products, and metabolic syndrome may also be associated with MCI in patients with type 2 diabetes [16, 21-23].

Some diabetes drugs can improve cognitive function. The DPP-IV inhibitor linagliptin improves diabetes-mediated cerebrovascular dysfunction by reducing plasma endothelioconstricting peptide -1(ET-1) levels and cerebrovascular hyperreactivity [24]. Epalrestat, Donepezil, empagliflozin and have protective effects against cognitive impairment through their antioxidant and anti-inflammatory effects [25, 26].

Hypertension

The treatment and control of hypertension is considered to be an important public health problem in the prevention of various cardiovascular and cerebrovascular diseases[27].According to authoritative epidemiological surveys, between 1990 and 2019, the number of people aged 30 to 79 with hypertension increased from 648 million (women: 331 million, men: 317 million) to 1.278 billion (women: 626 million and men: 652 million), but the global hypertension control rate by 2019 was only 23% for women and 18% for men[28].The brain and its function are one of the targets of long-term chronic hypertension. Hypertension not only damages the structural and functional integrity of cerebral microcirculation, destroys the blood-brain barrier, promotes neuroinflammation and deterioration of amyloid disease, but also causes some pathophysiological changes in cerebrovascular, such as vascular inflammation, oxidative stress, hypoperfusion caused by vascular stiffness,and higher levels of beta-amyloid plaques, atrophy, and neurofibrillary tangles in the brains of hypertensive[29]. Moreover, neuroradiological markers such as white matter hypersignal, lacunar infarction, microbleeding, and enlarged perivascular space are associated with the development of cognitive impairment.[30, 31]

Therefore, hypertension has been identified as a modifiable risk factor for cognitive dysfunction, including MCI [32-34].A multi-center study showed that the incidence of cognitive impairment was higher in hypertensive patients than in the general population, and executive function and semantic memory were the most affected cognitive domains [35]. Qin[36]conducted a meta-analysis on 47,179 participants, and the results showed that,the overall prevalence of MCI in hypertensive patients was about 30%, which was significantly higher than that in non-hypertensive elderly people. Wang[32] found in a 7-year retrospective cohort study that different grades and

duration of hypertension had different effects on the occurrence of MCI: reduced risk of mild cognitive impairment in subjects with grade 1 hypertension or duration less than 10 years (HR: 0.54), and subjects with grade 2-3 hypertension or a duration of 10 years or more had an increased risk of developing hypertension (HR: 1.75), meaning that mild or short-term hypertension may be a protective factor for MCI, but moderate to severe or long-term hypertension is a risk factor for MCI. This result may be due to a compensatory effect of early stage hypertension on vascular lesions and cerebral hypoperfusion.

Hypertension treatment can reduce cognitive decline to a certain extent [37-39]. A recent randomized clinical trial showed that intensive blood pressure control (systolic target < 120 mmHg) and standard blood pressure control (systolic target < 140 mmHg) reduced the risk of MCI, with less increase in leucoencephalopathy volume in the intensive treatment group[40, 41].Although decreased renal function as measured by eGFR may be a factor in the increased risk of MCI, but it is not associated with or without intensive hypertensive therapy. It means intensive hypertensive therapy does not lead to a decrease in eGFR [42].Antihypertensive drugs, especially calcium channel blockers and renin-angiotensin system blockers (ACEI and ARB), may help prevent cognitive decline by lowering blood pressure and neuroprotective mechanisms[38].

Hypercholesterolemia

Significantly elevated plasma total cholesterol increases the risk of MCI [43].A population-based 21-year follow-up study found that subjects with high cholesterol levels (≥6.5mmol/L) in middle age had an increased risk of developing MCI (OR, 1.9; 95% CI, 1.2-3.0). Hypercholesterolemia may affect the brain in two ways: on the one hand, hypercholesterolemia leads to high levels of amyloid beta deposition in the human brain [44]； On the other hand, high cholesterol indirectly increases the risk of cardiovascular and cerebrovascular diseases. In addition to sporadic hypercholesterolemia, a few scholars have begun to study familial hypercholesterolemia. Daniel[45] found that the prevalence of MCI in patients with familial hypercholesterolemia was significantly higher than in the control group, and far exceeded the prevalence predicted by epidemiological studies in the general population or sporadic hypercholesterolemia observed during follow-up. This may be related to the earlier onset of hypercholesterolemia.

Interestingly, in a six-year follow-up study, serum cholesterol and many major cholesterol-related lipoprotein markers decreased significantly in elderly patients with

MCI, while those with normal cognitive function showed an upward trend [46].The possible reasons for this phenomenon may be: The existence of cholesterol is crucial to synaptic maturation and maintenance of synaptic plasticity [47]. With the aging of the body, the cholesterol content in the brain gradually decreases, resulting in the decreased role of cholesterol in maintaining synaptic plasticity, and leading to the decline of cognitive function. However, the cholesterol level in the body of patients with normal cognition is still enough to maintain the synaptic plasticity. At the same time, cholesterol is also an important component of cell membrane, which acts as a regulator of ionic permeability and signal transduction. The reduction of cholesterol level may also weaken this function to some extent. The findings explain why statins, the most commonly used cholesterol-lowering drugs, have not been shown to prevent cognitive decline [48-50].

Hyperhomocysteinemia（HHcy）

HHcy is one of the modifiable risk factors for the occurrence and progression of MCI [51]. A Polish memory clinical study reported that [52],tHcy in MCI patients who converted to AD was higher than that in those who remained stable, suggesting that HHcy patients were more likely to transition from MCI to AD. Hcy is a sulfur-containing amino acid, which exists as an intermediate in the metabolic pathway of methionine and cysteine, and its mechanism of causing nervous system damage is as follows：（a）Hcy can catalyze autooxidation in the presence of oxygen molecules and promote the formation of reactive oxygen species (ROS) such as hydrogen peroxide, hydroxyl radicals and thiol radicals, which may cause cytotoxicity when the concentration of ROS is increased in vivo [53]；（b）As a glutamate receptor agonist, Hcy may cause brain excitotoxicity and induce oxidative stress or inflammation through nuclear factor kappa-β activation [54, 55]；（c）Hcy may also up-regulate the expression of MCP-1, IL-1β, IL-8, TNF-α and other inflammatory factors [56, 57]. Hcy can reduce plasma Hcy concentration through the re-methylation pathway and the sulfur transfer pathway, and the abnormality of any metabolic pathway will increase the plasma Hcy concentration.

The normal metabolic function of Hcy depends on the intake of folic acid, vitamin B6 and vitamin B12. The decrease in the concentration of these substances in the body is the key reason for the occurrence of HHcy. Supplementation of folic acid, vitamin B6 and vitamin B12 can effectively reduce the level of Hcy in the body[58]. Clinically, the elderly are more likely to be deficient in B vitamins, and it shows an upward trend

with age. Therefore, supplementation of folic acid, vitamin B6 and vitamin B12 can not only reduce the concentration of plasma Hcy, but also prevent cognitive decline in MCI patients. In a randomized controlled trial, [59] Smith gave two groups of 168 MCI patients older than 70 years folic acid, vitamin B 12, vitamin B6, and placebo, and found that the rate of atrophy was reduced in the treatment group. These results suggest that supplementation of these B vitamins may not only improve cognitive performance [60],but also slow the rate of global and regional brain atrophy in MCI participants[59, 61]. Compared with folic acid and vitamin B12 alone, the combination of folic acid and vitamin B12 showed better efficacy[62].Folate as a methyl donor can provide methyl groups for Hcy methylation[63],Vitamin B12 plays a role as a coenzyme of methionine synthase in the methylation process. Vitamin B6 can activate the sulfur transfer pathway and transfer sulfur from homocysteine to cysteine, which can use the transferred sulfur to synthesize glutathione with itself, and the reduction of glutathione can enhance the antioxidant effect of the organism[64].

Smoke

In older MCI patients, smokers have a more rapid decline in functional performance than nonsmokers, which is associated with a more rapid decline in inner nasal skin mass over time[65]. Sleep duration played an important mediating role in the association between smoking and MCI[66]. Smokers were more likely to have sleep problems compared to non-smokers. Because some smokers may smoke at night due to the onset of nicotine withdrawal symptoms, waking up at night to smoke seems to disturb sleep [67]. One of the problems with sleep is sleep deprivation, which leads to short sleep duration, fatigue, cognitive decline and reduced sleep duration [68]. There was a U-shaped association between sleep duration and cognitive decline, meaning that short or long sleep duration was accompanied by a higher risk of cognitive impairment events [69].

Long-term smoking is associated with elevated brain oxidative stress (oxS), which plays an important role in reducing sleep duration [70]. At the same time, melatonin secretion from the pineal gland is continuously reduced, which can continuously impair cognitive function in animals or humans [71]. Inefficiency of Aβ removal caused by smoking may also contribute to MCI. Smoking also affects the function of cortico-striatal circuits. Cognitively normal smokers had increased functional connectivity between dorsal striatum and parietal regions compared to non-smokers, whereas MCI smokers showed reduced functional connectivity between dorsal

striatum and paricooccipital regions and increased functional connectivity between ventral striatum and frontal cortex compared to cognitively normal smokers and non-smokers with MCI. It is suggested that smoking affects the function of cortico-striatal circuits in MCI patients, and this effect may damage the function of cortico-striatal circuits by aggravating Aβ pathology[72]. Smoking affects visual attention through cortico-striatal circuits, which further leads to memory decline in MCI patients [72]. The cortical-striatal circuit may be a potential therapeutic target for smoking [73]. Other studies have shown that chronic nicotine exposure may lead to the destruction of functional connectivity between the basal ganglia of Meynert and the precuneus in MCI patients, suggesting that the precuneus may also be an important target for smoking to affect cognitive function in MCI [74].Therefore, smoking cessation can reduce the cognitive impairment of smoking through a variety of ways and improve cognitive status [75].

Health of the lungs

Evidence suggests that impaired lung health may be associated with dementia and cognitive deterioration. Impaired lung function (e.g., vital capacity, forced expiratory volume in 1 second, and maximum expiratory flow) is increasingly recognized as a predictor of cognitive performance [76],and poor lung function is associated with an increased risk of MCI [77]. One of the most common causes of impaired lung function is chronic obstructive pulmonary disease (COPD).COPD is a progressive but treatable and preventable disease. 210 million people worldwide have been diagnosed with COPD and it is projected to become the third leading cause of death by 2030 [78]。In a follow-up study of 1425 cognitively normal individuals aged 70-89 years, COPD significantly increased the risk of MCI, especially non-amnestic MCI (NA-MCI) (hazard ratio 1.83), and there was a dose-response relationship between COPD duration longer than 5 years and MCI risk [79]。Smoking can increase the risk of MCI through multiple pathways, mainly mediated by chronic hypoxemia. Pulmonary dysfunction caused by COPD can reduce oxygen supply to the brain and affect brain energy metabolism, thus promoting cerebral ischemia and inducing oxidative stress, leading to oxidative stress-mediated damage, accelerating vascular damage and degenerative diseases. Chronic hypoxemia also induces systemic inflammation. Patients with hypoxemia have elevated levels of systemic inflammatory markers, including interleukin-6, C-reactive protein, leukotriene B4, tumor necrosis factor-α, and interleukin-8 [80, 81],These inflammatory markers are associated with cognitive

dysfunction. In addition, physiological stress, cerebral artery stiffness and small vessel injury can also impair cognitive function [76, 82]. In animal experimental models of acute lung injury, olaparib[83] and dimethyl fumarate [84] have been found to inhibit systemic inflammatory response and protect cognitive function. Inflammation may be a target for the treatment of cognitive impairment caused by lung health problems. Long-term physical exercise can not only exercise respiratory muscles and improve ventilation, but also achieve systemic anti-inflammatory effects [85, 86].

Education

Education level is an important factor affecting the occurrence of MCI, and healthy elderly people with higher education have better cognitive performance than those with lower education. [87] Cognitive reserve (CR) is used to account for individual differences in brain networks that are resistant and resilient to neuropathological processes over time [88]. Highly educated individuals are better able to resist cognitive decline caused by pathological changes in the brain than those with low education levels. In brain electrical activity, high CR may produce a neuroprotective effect by enhancing rsEEGα source activation [89]. In a 7-year, population-based longitudinal study, WML significantly increased the risk of MCI among participants with low education levels. More educated subjects are thought to be more likely to withstand the harmful effects of severe WML, possibly because those with high education levels have higher cognitive reserve than those with low education levels, and those with low education levels have higher cognitive reserve. And mitigated the impact of WML on the risk of developing MCI [90].

The preventive effect of education on MCI dementia can also be explained by the brain reserve theory, which states that the brain responds to the pathological changes of cognitive impairment by enriching neurons and synapses[91]. The greater myelination and richer fasciculation observed in the white matter of highly educated individuals[92],as well as improving neural resources in childhood and young adulthood by increasing synaptic density, and then attenuating the effects of neurological decline caused by aging or age-related diseases[93]. These augur well for educational engagement in the early stages of life, which may reduce the occurrence of cognitive impairment and dementia in later life, reduce the associated individual and societal costs, and enable them to withstand more cognitive decline [94]. Education not only reduces the occurrence of MCI, but also protects the further deterioration of cognitive function in the early stage of cognitive impairment and reduces the

conversion rate of MCI patients to dementia [95, 96]。In a neuropsychological evaluation of 249 aMCI patients at 31 clinics, it was found[97] that higher education was protective against cognitive decline in early aMCI, but the higher risk of AD transformation in late aMCI than in early aMCI meaning that this protective effect was lost in late stage.

Depression

Depression is a common psychiatric symptom in patients with MCI or AD [98]. Depression increases the risk of developing MCI in cognitively normal individuals [99]. Many studies have reported that impaired cognitive function is associated with depression in patients with MCI[100-102].Feng[103] found that diffusion tensor imaging (DTI) of patients with early MCI (EMCI) without depression, patients with EMCI with mild depression (EMCID), and patients with late MCI (LMCI) without depression, compared with healthy controls, The average brain controllability of default mode network (DMN) was significantly decreased in EMCI, LMCI and EMCID groups (P < 0.05). The mean controllability of DMNS in EMCI and LMCI groups was also significantly higher than that in EMCID group. Another study found that MCI participants with depression showed greater deficits in both immediate and delayed memory than non-depressed participants A systematic review of 34 longitudinal studies reported that people with depression had greater cognitive decline in old age than those without depression, and found that memory loss, executive function, and information processing speed decreased over time[104].On cognitive tests, patients with MCI and depression scored lower than those with MCI alone[105].

There is evidence that depression confers a higher rate of progression of neurodegenerative diseases from MCI to dementia[106-108]. A meta-analysis of 18 studies found that the pooled relative risk of progression to dementia was 1.28(P =.003) in MCI subjects with depressive symptoms compared with those without depressive symptoms. [109]. This may be related to the fact that depressed patients have more amyloid abnormalities than non-depressed patients [110],and the increased risk of neuropsychiatric symptoms caused by MCI with brain Aβ load [111]. However, a 3-year prospective study of outpatients with MCI showed no increased risk of AD in patients with depressive symptoms [112]. The reason for this opposite conclusion may be that the study did not consider the duration of depression, onset of depression, treatment or not. Because Spalletta et al. [113] reported that persistent or incidental depression worsened cognitive outcomes in patients with early AD, whereas

depression without depression or recovery did not affect cognitive outcomes. In addition, patients with MCI are more likely to develop depression compared to those without MCI [114]. Studies have shown that exercise interventions, such as extensive aerobic exercise [115]、Tai Chi qigong [116] and Baduanjin [117] , can improve the level of cognitive function in elderly patients with MCI. However, these studies have focused on MCI, and little is known about the treatment of MCI patients with depression. In recent years, there is no evidence to support the effectiveness of antidepressants in the treatment of MCI patients [118]. There are few studies on the psychological effects of game training on the elderly with MCI, and the training is designed based on stimulation of the cerebral cortex to improve the cognitive function of patients and reduce the risk of MCI and depression [119].XUE[120] et al., after 8 weeks of game training for patients with MCI and depression, found that the cognitive and depression scores of the participants were significantly improved（$p<0.05$）.

Anxiety

The current study established that anxiety can increase the incidence of MCI [121, 122].Smith et al. [121] investigated 32,715 individuals aged ≥50 years in six countries and found a positive correlation between anxiety and MCI (OR 1.35-14.33), suggesting that elderly patients with anxiety disorders are at high risk of MCI. The reason for this may be that anxiety may reduce intellectually stimulating activities, increase sleep problems, and increase the risk of cognitive decline with benzodiazepine use. Anna[122] found that Aβ deposition and anxiety synergistically increased the risk of MCI (joint effect HR6.77), and in addition, coexisting MCI with elevated Aβ deposition was associated with higher odds of anxiety and depression. The co-occurrence of MCI and anxiety increases the possibility of MCI transforming into dementia, especially AD [123, 124]. A systematic review and meta-analysis determined that the pooled relative risk of progression to dementia was 1.18 for MCI patients with anxiety compared with those without anxiety [125]. At the same time, MCI patients can also promote the occurrence of anxiety symptoms [126, 127],and the two can be said to interact. Chen et al [126] determined that the prevalence of anxiety in community MCI patients was 14.3% and that in clinical MCI patients was 31.2%. Good lifestyle habits, such as physical activity [128]、healthy diet [129]、moking cessation [130]和 nd psychological interventions [131],as well as art therapy (AT) and music recall activities (MRA) [132] can reduce anxiety and reduce the incidence of MCI.

Conclusion

Vascular risk factors, lung health, education and mental factors promote the occurrence or development of MCI in the elderly. It is not difficult to find that the impact of these factors on cognitive function can be mitigated, thereby reducing the incidence of MCI or even progression to dementia by understanding the mechanism of action of them and appropriate drug or non-drug treatment. The interventions we reviewed were not difficult to implement, which meant that they were practical, with low requirements for medical conditions and low investment of health care resources. However, there may be more modifiable risk factors than the above, and further research is needed to find and develop effective intervention measures.

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