

## Chinese Expert Consensus on the Prevention and Treatment of Cognitive Disorder

(Expert Group of Chinese Expert Consensus on the Prevention and Treatment of Cognitive Disorder, Shanghai 200000)

### Basic concept of cognitive disorder and dementia

**Cognitive function and cognitive disorder** Cognition is one of the human mental activities, and refers to a mental process of an individual to know and understand a thing. It includes simple determination of oneself and environment, perception, attention, learning and memory, thinking and language. The executive function means the ability to effectively start and finish a purposeful activity decided by oneself. The executive function is a complex process, including planning, starting, effectively executing purposeful activities and self-regulation and involves planning, starting, sequence, operation, feedback, decision making and judgment.

The cognitive function consists of several cognitive domains, including memory, calculation, temporal/spatial orientation, structural capability, executive capability, language understanding & expression, and application. In the clinical practice, the above aspects can be obtained by asking the patients, and sometimes, relevant situations can be supplemented and checked by asking their caregivers. The overall cognitive function and specific cognitive domains of an individual may be evaluated quantitatively, and some cognitive impairments that are difficult to detect in daily life may also be found by various neuropsychological examinations and tests.

Cognitive disorder refers to various degrees of cognitive impairments caused by various reasons in general, from mild cognitive impairment to dementia. Cognitive disorder is also known as cognitive hypofunction, cognitive deficit or cognitive disability.

**Mild cognitive impairment (MCI) and its typing** It refers to a clinical status between normal aging and mild dementia for an individual with memory disorder and (or) other mild cognitive disorders. But the individual's social occupation or daily life function are not affected and also cannot be explained by known medical or neurological and psychotic diseases.

The early definition of MCI is a progressive memory impairment similar to Alzheimer's disease (AD), which emphasizes the disease state, and refers in particular to the preclinical phase of AD. In addition, MCI may be also manifested as language, attention and spatial ability impairment. However, MCI does not represent a pre-AD state only anymore after it's considered as a transitional stage between normal aging and dementia. Therefore, MCI may be divided into two types: amnesic MCI (aMCI) and non-amnesic MCI. aMCI is a typical definition, including simple memory impairment and memory with other cognitive impairments, and mainly refers to the early stage of AD. The non-amnesic MCI includes single non-memory domain impairment and several non-memory domain impairments, and is a general MCI, covering multiple cognitive impairments and may be an early manifestation of several kinds of dementia. MCI may also be classified as degenerative MCI and vascular MCI according to the pathogeny. MCI has many outcomes.

**[About the corresponding author]** Li Yansheng (1961-), male, professor, from Nanjing

The most important clinical significance of determining MCI is early detection and early intervention to delay or prevent the occurrence and development of dementia.

**Dementia and its typing** Dementia refers to the clinical syndrome of a group of serious cognitive defects or hypofunctions caused by organic diseases, such as progressive thought, memory, behavior and personality disorders, can be accompanied with mental and motor function symptoms, and the damage can reach a degree that affects occupation, social function or daily life abilities.

There're many typing criteria for dementia. The most common typing is etiological typing. Dementia can be classified as degenerative dementia, vascular dementia (VaD), inflammatory dementia, infectious dementia, and dementia caused by tumor and othe reasons. AD, VaD and mixed dementia are clinically most common types with the highest incidence.

Mixed dementia refers to the coexistence of AD and VaD, typically manifested as new rapid-onset cognitive impairment of AD patient after the attack of cerebral infarction. However, recent studies showed that many AD patients have vascular risk factors and cerebrovascular disease evidence on imaging and pathology, making it difficult to clinically determine whether cerebrovascular diseases directly cause dementia or aggravate the pathophysiologic effects of AD. The concept of AD with cerebrovascular disease is probably more scientific and rigorous than mixed dementia.

### **Current situation and development direction of the prevention and treatment of cognitive disorder in China**

**Epidemiological features of cognitive disorder** Age is the most important factor influencing the incidence of cognitive dysfunction, and the incidence of cognitive disorder quickly increases with age. Cognitive disorder has a certain association with gender. AD is more common in females, while VaD is more common in males. The incidence and morbidity of dementia in Chinese population (4.8% for population > 65 years) is comparable to that in western countries. The risk of the population with aMCI converted to dementia is much higher than that in population with normal cognition. There's no consistent investigation result in the influence of the difference between urban and rural areas.

**Risk factors of cognitive disorder** Known risk factors of cognitive disorder include: demographic factor (age, gender and family history, etc.), genetic factor (apolipoprotein E4, presenilin 1, presenilin 2, tau protein,  $\beta$  amyloid precursor and Notch3 gene, etc.), lifestyle (smoking, unreasonable diet, lack of exercise and social withdrawal, etc.), and personal history (undereducation, head trauma and mental diseases, etc.). Recently, the significant finding is that various vascular risk factors (atherosclerosis, stroke, hypertension, coronary heart disease, atrial fibrillation, dyslipidemia and diabetes mellitus, etc.) are risk factors of not only VaD, but also AD and MCI.

**Development direction of the prevention and treatment of cognitive disorder in China** Firstly, popularize relevant knowledge to make more healthcare staff and the public aware of the harms and prevention and treatment significance of cognitive disorder.

Raise the awareness of the role of vascular risk factors in cognitive disorder, standardize the management of vascular risk factors, and effectively achieve the primary prevention of cognitive disorder. Strengthen the

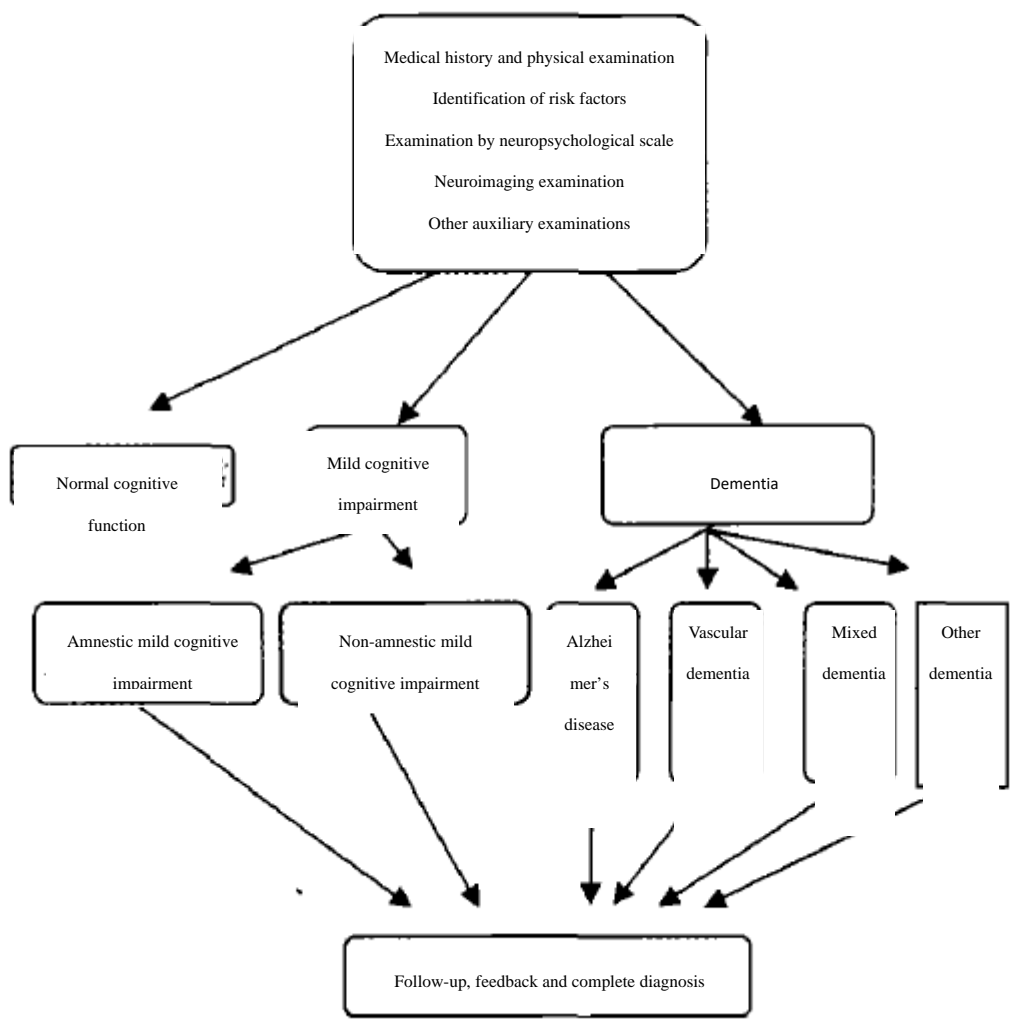
study of basis and standard of early diagnosis of cognitive disorder, implement early detection and early intervention and achieve effective secondary prevention.

Standardize the prevention and treatment measures of cognitive disorder, stick to the principle of early treatment and lifelong treatment, focus comprehensively on the cognition, mind and behavior of the patients, and pay attention to the quality of life of patients.

The prevention and treatment of cognitive disorder is a systematic project involving the society, economy, medicine and family, and shall be paid attention to and supported by the whole society.

### Diagnosis of cognitive disorder and dementia

Diagnosis procedure of cognitive disorder and dementia



**Diagnosis of mild cognitive impairment** The clinically common diagnostic criteria of aMCI are summarized as follows: ① complain mainly about memory disorder and confirmed by an informant; ② other cognitive functions are relatively good or mildly impaired; ③ daily life ability is not affected; ④ fail to meet the diagnostic criteria of dementia; ⑤ other systemic diseases that may cause brain hypofunction have been ruled out; ⑥ 2-3 scores for the global deterioration scale (GDS), 0.5 scores for the clinical dementia scale (CDR), < 1.5 SD for the memory test score in age and education matched control group, and at least 24 scores for

MMSE, or at least 123 scores for Mattis dementia rating scale (DRS).

**Diagnosis of dementia** DSM-IV criteria or ICD-10 criteria are recommended (details omitted). (1) Diagnosis of AD dementia: the diagnostic criteria of AD dementia in DSM-IV are recommended (details omitted). The diagnostic criteria of AD as “possible”, “very possible” and “definite” specified by NINCDS-ADRDA are recommended (details omitted). (2) Diagnosis of vascular dementia (VaD): the diagnostic criteria of VaD in DSM-IV are recommended (details omitted). The diagnosis criteria of VaD as “possible”, “very possible” and “definite” specified by NINDS-AIREN are recommended (details omitted). (3) Diagnostic criteria of mixed dementia: a patient with AD and vascular dementia shall be diagnosed with mixed dementia, and the diseases causing the dementia shall be listed, for example, “mixed dementia due to possible vascular disease”, or “mixed dementia due to definite vascular disease”. The proportion of patients diagnosed with mixed dementia will increase with the development of the diagnostic means. (4) Diagnostic criteria of other dementia: omitted.

**Auxiliary diagnosis method** Neuropsychological test is an important diagnosis method of cognitive disorder, and different scales shall be selected for evaluation as appropriate, for example, screening scales (MMSE, etc.), comprehensive evaluation scales (Wechsler adult intelligence scale, CDR, GDS, and Alzheimer disease scale, etc.), specific cognitive function examinations (memory and executive functions, etc.), mental and behavior scales (neuropsychiatric questionnaire, Hamilton depression scale and old people depression scale, etc.).

The neuroimaging examination is very important for diagnosis and differential diagnosis. Head MRI shall be performed, and SPECT, PET and functional MRI examination may be performed if the conditions permit.

The blood routine, liver function, renal function, thyroid function, folic acid level and vitamin B<sub>12</sub> level shall be tested routinely. The examination of tau protein and APP in the cerebrospinal fluid helps the diagnosis. The electrophysiological examinations such as electroencephalogram and cognitive evoked potential may be performed.

The neuropathological examination and genetic examination may improve the accuracy of the diagnosis.

### **Prevention and treatment of cognitive disorder**

Basic principles of prevention and treatment of cognitive disorder

1. Actively identify and control various risk factors, particularly the controllable vascular risk factors, to reduce the incidence of cognitive disorder.
2. Early diagnosis of MCI, active intervention and early treatment.
3. Effectively treat some controllable cognitive disorder with definite pathogeny, such as cerebrovascular disease, cerebral trauma, inflammation, hydrocephalus and systemic disease.
4. Actively perform symptomatic treatment to improve cognitive function according to the requirements of evidence-based medicine.
5. Pay attention to the intervention of mental and behavioral abnormality.
6. Actively carry out non-medicine treatments, such as psychotherapy and cognitive-behavioral therapy.
7. Pay attention to the treatment of the complications and concomitant diseases.
8. Strengthen the rehabilitation training.
9. Pay attention to the quality of life of the people being taken care of.

### **Drug therapy of cognitive disorder**

1. Therapeutic drugs supported by evidence-based medicine: (1) cholinesterase inhibitor: the cholinergic pathway of central nervous system is a processing and storage center of memory and cognition information. Enhancing the function of the cholinergic transmitter system is an important treatment method of AD, and such kind of drug has a definite effect of delaying the disease progression and improving clinical symptom. At present, it's the drug of first choice for AD, and is also applicable to the vascular dementia, Lewy body dementia, Parkinson disease with dementia and dementia caused by cerebral trauma. ① Donepezil: it has a highly selective and reversible inhibition effect on acetylcholin esterase, and can improve the cognitive status and daily life ability of patients with AD and VaD when administrated long-term. ② Rivastigmine: it can inhibit both acetylcholin esterase and butyrylcholinesterase, has good efficacy in clinical application. It is a common drug for AD treatment at present, and its dose shall be increased gradually in clinical application. ③ Galanthamine: it has the effects of inhibiting acetylcholin esterase and regulating cholinceptor, and is effective to improve the cognitive function and daily life ability of patients with mild and moderate AD and VaD. (2) Excitatory amino acid antagonist: Memantine can antagonize N-methyl-D-aspartate receptor, prevent the release of glutamate, reduce the excitatory toxicity, and be used to treat patients with middle-advanced stage AD. (3) Calcium antagonist: Nimodipine is a slow channel voltage-dependent  $Ca^{2+}$  antagonist for treating AD, VaD and mixed dementia, It can improve the clinical overall evaluation and cognitive function of patients, delay the development of cognitive disorder of VaD patients and reduce the incidence of vascular adverse events.
2. Clinically common therapeutic drug: (1) cholinesterase inhibitor: huperzine A is alkaloid extracted by the Chinese researchers from the serrate clubmoss herb of huperziaceae for the first time. It is a reversible and selective acetylcholinesterase inhibitor and can improve the symptoms of dementia patients. (2) Ergot alkaloid: it increases the cerebral blood flow and energy metabolism by antagonizing the effect of epinephrine, It can possibly improves the cognition, emotion and self-care ability of daily living of AD and VaD patients. (3) Pyrrolidine drugs: they can improve the cerebral microcirculation, help energy metabolism, improve the learning and memory ability, and have low adverse reactions when administrated long-term, and they are considered as anti-dementia drugs in some countries. (4) Antioxidant: the ginkgo leaf preparation can improve the cerebral blood circulation and amino acid receptor antagonism effect, protect brain function and also be used for the treatment of dementia with good safety, but the evidence from random control clinical trials is inadequate. Vitamin E, vitamin C and L-Deprenyl have an antioxidation effect, but the evidence from the relevant random control clinical trials is inadequate, and their prevention effect is possibly higher than the cognition improvement effect. (5) Non-steroidal anti-inflammatory drugs: the epidemiological survey data shows that the use of non-steroidal anti-inflammatory drugs, such as aspirin and ibuprofen, can reduce the risk of AD, but the recent clinical trial results on epoxidase-2 inhibitor are different. (6) Estrogen replacement therapy: the epidemiological survey data also shows that the estrogen replacement therapy can significantly reduce the risk of AD among menopause women, and some clinical trials think that it may delay the disease progression and improve cognitive function. However, recent large-sample-size clinical trials raise an objection to that, and particularly the long-term use safety is questioned. (7) Statins: they have lipid regulation and anti-inflammatory effects, and can decrease cardiac-cerebral vascular events, but clinical trials on dementia treatment are absent.
3. Therapeutic drugs for controlling vascular risk factors: much epidemiological evidence has proven that effective control of the vascular risks factor can delay cognitive hypofunction and reduce the incidence of dementia. Therefore, hypertension, hyperglycemia and dyslipidemia should be controlled actively and strictly, relevant drugs should be reasonably selected according to the requirements of evidence-based medicine, and the anti-platelet aggregation and anticoagulation therapies should be paid attention to.

The development of cognitive disorder is a long-term process, and possibly starts a few decades ago clinically. Treatment at a late stage of disease progression, particularly after dementia, may still delay the progression of cognitive hypofunction, but the existing injuries cannot be reversed. Therefore, the early intervention has important significance. MCI is an entry point of early detection and early intervention. The particular intervention measures are under exploration.

Though certain treatment means are present for various kinds of dementia, the problems of poor efficacy and high cost still exist. Prevention shall be the most important measure. Among various risk factors, the vascular risk factor can be found and controlled. Therefore, special attention shall be paid to the screening and intervention of high risk populations. Patients with hypertension, cerebral atherosclerosis, cerebrovascular disease, diabetes mellitus a coronary heart disease shall undergo memory and intelligence examination to achieve early detection and early treatment. The earlier the treatment, the better the efficacy.

Experts in the Expert Group of Chinese Expert Consensus on the Prevention and Treatment of Cognitive Disorder (in order of surname pinyin): Chen Shengdi, Fan Dongsheng, Gao Xuguang, He Maolin, Jia Jianping, Li Shunwei, Li Yansheng, Luo Benyan, Tang Cimei, Wang Xin, Wang Lijuan, Wang Luning, Wang Muyi, Wang Shaoshi, Wang Xinde, Wang Yinhua, Wang Yongjun, Xu Xianhao, Zhang Weiwei, Zhang Zhenxin, Zhang Zhuo, Zhao Zhongxin, Zhou Shengnian, etc.

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