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Pathogenesis, Rehabilitation Assessment, Treatment Status, and Research Progress of Vascular Dementia

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Abstract: Given the global trends in population aging, the prevalence of vascular dementia (VD) is increasing year by year. VD has become the second most common type of dementia and can seriously threaten the quality of life of patients. Since VD is preventable, it is important to study VD clinically in order to improve the prognosis of patients. In recent years, a large number of studies have been carried out at home and abroad, focusing on the pathogenesis, rehabilitation assessment, and treatment of VD. This article is a concise overview of these studies.

Keywords: Vascular dementia; Rehabilitation assessment; Pathogenesis; Treatment

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1. Introduction

Vascular dementia (VD) is a clinically common chronic progressive intellectual impairment syndrome, which is mainly caused by cerebrovascular disease or damage to brain tissue and characterized by memory, social life ability, cognitive ability, and other dysfunction. VD has high morbidity, a stepwise progression, and can seriously reduce the quality of life of patients as well as increase the economic burden of their families [1,2]. In recent years, with the global trends in population aging, the incidence of VD is also increasing, and the survival rate among women is higher than that among men [3]. Since VD is reversible and treatable, early clinical intervention plays a very important role in improving the prognosis [4]. The aim of this study was to review the pathogenesis, rehabilitation assessment, treatment status, and research progress of VD in order to provide reference for the diagnosis and treatment of VD in the late clinical stage.

2. Pathogenesis of vascular dementia

The pathogenesis of VD mainly includes molecular mechanism and genetic mechanism.

2.1. Molecular mechanism

The molecular mechanism includes cholinergic pathway disorder, nitric oxide, negative event cascade reaction, *etc*. VD is mainly a group of syndromes associated with vascular disease and intellectual impairment. Therefore, the occurrence and progress of VD are closely related to abnormal molecular mechanisms related to brain function (nervous system development, learning, and memory).

2.1.1. Cholinergic pathway disorder

The hippocampal loop cholinergic pathway plays a very important role in brain memory and information storage. Acetylcholine is unstable and is easily hydrolyzed. Therefore, when evaluating cholinergic conditions clinically, it is necessary to detect not only the acetylcholine content, but also the key enzyme acetylcholine transferase, which is used to synthesize acetylcholine. Studies have shown that when the level of acetylcholine transferase in the hippocampus decreases in patients with VD, learning and memory decline, and it has a close relationship with the severity of the disease [5].

2.1.2. Calcium ion, calmodulin, and its dependent protein kinase II in the hippocampus

Studies have shown that there is a close relationship between degenerative pathological changes and calcium ion metabolism disorders [6]. As an intracellular calcium sensor, calmodulin not only affects cell function by regulating intracellular calcium ion content, but also combines with activated calmodulin-dependent protein kinase II to form memory and storage mechanisms. The abnormal activation of calmodulin-dependent protein kinase II in VD patients will cause damage to neurons and lead to cognitive dysfunction.

2.1.3. Change in synaptic plasticity

Synaptic plasticity serves as an important physiological basis in learning and memory, mainly through long-term enhancement and suppression. In the pathogenesis of VD, the change in synaptic plasticity is not conducive to the development and repair of the nervous system, as well as learning and memory [7].

2.1.4. Nitric oxide

Nitric oxide is mainly produced by the catalysis of nitric oxide synthase, which participates in various physiological processes (peroxide formation, inflammatory damage, synaptic plasticity, neuronal excitotoxicity, long-term potentiation process, *etc*.). It affects the calcium pathway of learning and memory and thus interferes with learning and memory functions. Studies have shown that the increase in nitric oxide synthase level is one of the important pathological mechanisms leading to the occurrence of VD [8].

2.1.5. Renin-angiotensin-aldosterone system

Angiotensin II receptors (hippocampus) may be overexpressed in brains with low perfusion, contributing to neuronal damage and triggering the occurrence of VD.

2.1.6. Negative event cascade

Negative event cascade mainly includes excitatory amino acid toxicity, inflammatory response, oxidative stress, and so on.

Excitatory amino acids mainly include N-methyl-D-aspartic acid, aspartic acid, quinolinic acid, glutamic acid, *etc*. Among them, N-methyl-D-aspartic acid plays an important role in long-term potentiation. When it is activated by a high concentration of glutamic acid, it can hinder the transmission of information between synapses in the hippocampus, resulting in a decline in learning and memory. In addition, high levels of glutamate can also lead to mitochondrial toxicity, calcium overload, *etc*., which may result in brain energy disorders and neuronal damage.

Cerebrovascular disease may lead to cognitive impairment, accompanied by inflammatory response, oxidative stress damage, *etc*., resulting in the release of large amounts of inflammatory mediators (tumor necrosis factor α, interleukin 1β, transforming growth factor β, *etc*.) and the reduction in antioxidant substances. Studies have shown that interleukin 6 is abnormally elevated in the cerebrospinal fluid of VD patients and can be used as one of the sensitive biomarkers of VD [9]. According to research, during the

pathogenesis of VD, oxidative stress markers in the blood will change, *i.e.*, the content of antioxidant substances such as vitamin C and vitamin E will decrease, and the level of oxidative damage products will increase [10].

2.2. Genetic mechanism

NOTCH gene and apolipoprotein E are clinically recognized VD pathogenic genes. Among them, the *NOTCH3* gene can be regarded as a relatively common VD-causing mutation gene, mainly because the mutation of cysteine effect can lead to the misfolding and aggregation of Notch3 protein and then cause the mutation of *NOTCH3* gene. Apolipoprotein E can be considered as one of the potential pathogenic genes of VD. Studies have shown that polymorphisms of apolipoprotein E are closely related to the occurrence and development of VD [11].

3. Rehabilitation assessment of vascular dementia

Taking into account of the clinical characteristics of VD, its main rehabilitation assessment includes the overall assessment of cognitive function, the assessment of various aspects of cognitive impairment, the assessment of mental and behavioral symptoms, and the assessment of daily life function.

3.1. Overall assessment of cognitive function

In VD assessment and etiological analysis, the overall assessment of cognitive function plays a very important role. At present, the more commonly used clinical assessment scales include the Montreal Cognitive Assessment Scale (high specificity, sensitivity, and accuracy), the Hasegawa Dementia Scale (wide application range), and the Mini-Mental State Scale, which has high operability and validated clinical value.

3.2. Assessment of various aspects of cognitive impairment

The assessment of cognitive impairment mainly includes the assessment of memory function, attention, speech function, visuospatial ability, agnosia, and apraxia [12]. When evaluating the type, cause, and memory function of VD patients, the assessment of memory function is very important. The commonly used clinical assessment scales include the Wechsler Memory Scale and the Clinical Memory Scale, which can be used to measure the memory of patients. In the assessment of attention, the picture method, letter method, visual tracking, *etc*. can be used in clinical practice. One of the common symptoms of VD is aphasia. The commonly used assessment tools include the China Rehabilitation Research Center Aphasia Examination and the Chinese Aphasia Complete Test, which are easy to operate and reliable, as well as have been widely used in clinical practice. Early clinical assessment of whether VD is accompanied by agnosia and apraxia is essential for the later treatment of patients and prognostic improvement. The commonly used assessment tools include the Agnosia-Apraxia Rating Scale and the Cambridge Face Memory Test, which are simple and convenient for clinical application. VD may also be accompanied by symptoms of decreased visual-spatial ability during the onset. Clinically, the clock drawing test, building block composition test, free drawing test, and other tests are commonly used for assessment.

3.3. Assessment of daily life function

In order to meet the needs of daily life, it is very important for people to have the necessary functions. At present, the commonly used assessment scales in clinical practice include the Barthel Index, activities of daily living scales, the Functional Independence Measure, the Disability Assessment for Dementia Scale, *etc*. [13].

3.4. Assessment of mental and behavioral symptoms

At present, the Neuropsychiatric Symptom Questionnaire and the Dementia Behavior Rating Scale can be used to evaluate the mental and behavioral symptoms of VD. They are used not only to evaluate the presence or absence of symptoms, but also to evaluate the severity, frequency, and family burden of the symptoms.

3.5. Other common functional assessments

Since VD can also be accompanied by clinical manifestations such as balance disorders and abnormal gait, the Timed Up and Go Test, Berg Balance Scale, 10-Meter Walk Test, and human balance tests are also used to assess patients.

4. Treatment of vascular dementia

Due to the different types of VD, the clinical manifestations of patients are different. Therefore, the current clinical treatment of VD is mainly to provide individualized treatment, including but not only limited to therapeutic drugs (donepezil hydrochloride, Polygala saponin, cholinesterase inhibitors, antioxidants such as butylphthalide and curcumin, calcium ion antagonists such as nimodipine and angelica polysaccharide, alprostadil, piracetam, *etc*.), but also acupuncture, hyperbaric oxygen, and other treatments that focus on functional rehabilitation [14].

4.1. Cognitive function therapy

Cognitive function therapy can be divided into memory disorder treatment, attention disorder treatment, speech disorder treatment, agnosia and apraxia treatment, and so on. Among them, the treatment of memory impairment is mainly to provide targeted memory training according to the patient's memory impairment (type, degree, *etc*.). The methods include associative memory method, mobile terminal treatment technology, acupuncture technology, virtual reality (VR) technology, *etc*. Attention can be used as the basis for the completion of cognitive processing, so attention training is very important in improving the life of VD patients. Clinically, guesswork, time assignment, VR technology, neurofeedback training, and other training methods are commonly used to enhance attention and improve the effect of rehabilitation. At present, clinical methods such as the promotion of communication effect, finger acupoints, Schuell's stimulation, magnetic stimulation, and block removal are used to improve patients' speech function and have been clinically proven to produce significant curative effect. There are many methods for the treatment of agnosia and apraxia in patients with VD, including tapping, hot and cold stimulation (in case of unilateral neglect), recognition training and compensatory training (in case of visual-spatial agnosia), jigsaw auxiliary training (in the case of tactile agnosia), chain technique (in the case of mental apraxia), jigsaw puzzle and peg disk design training (in the case of structural apraxia), proprioception and motor stimulation (in the case of motor apraxia), *etc*. [15].

4.2. Treatment of mental and behavioral symptoms

During the onset of VD, patients often have psychological and behavioral symptoms such as anxiety and hallucinations, which may worsen the prognosis of patients. Currently, the commonly used clinical methods include Morita therapy, behavioral and psychological treatments (cognitive behavioral therapy, bright light therapy, *etc*.), and psychological homework training (emotional catharsis, cultivating interests, *etc*.).

4.3. Daily life function training

During the onset of VD, the training of patients' ability to carry out activities of daily living plays a very important role in maintaining their self-care ability. Initially, functional training of daily living can help

improve patients' daily living function. However, as the disease progresses, compensatory training can be applied instead and supplemented with behavior modification therapy. When it is difficult to improve patients' function, the treatment can be directed on the self-care ability of patients by making self-help tools and improving the environment.

4.4. Other treatments

For VD patients with balance disorders and abnormal gait, balance function training can be carried out to improve their ability to maintain balance. The methods include balance board and parallel bar training, endurance training, walking training, artificial intelligence equipment, *etc*.

5. Conclusion and prospects

VD is a series of complex pathological and physiological processes caused by cerebrovascular diseases. At this stage, the pathogenesis of VD has not been clarified. However, molecular mechanism and genetic mechanism have been proposed. Although VD cannot be completely cured, a comprehensive management including reasonable and effective rehabilitation assessment, with the use of drugs and rehabilitation training, can help improve the prognosis of patients. With the advancement and development of rehabilitation medical technology in recent years, further clinical research on the pathogenesis of VD, improvement of assessment, and treatment plan is the direction to improve the prognosis of patients and their quality of life. Based on this, expanding the sample size and unifying research methods in future research are new goals for in-depth analysis and standardization of VD management. The aim of this review was to provide a concise overview of the pathogenesis, rehabilitation assessment, and treatment of VD as reference for the diagnosis and treatment of VD, thereby laying a foundation for future research.

Disclosure statement

The author declares no conflict of interest.

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