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Vascular Dementia: from Pathogenesis to Treatment

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Abstract: ***Vascular dementia is the second most common type of dementia and a preventable disease, but its complex etiology and difficult diagnosis make it occupy a high status in the field of neuroscience and geriatrics. At present, modern medicine mainly takes oral donepezil and other drugs to control vascular risk factors and improve cognitive function (non-) drugs; summarizes the epidemiology, related factors, pathogenesis, treatment plan and future direction of vascular dementia.***

Keywords: Vascular dementia, Epidemiology, Pathogenic factors, Pathogenesis, Treat**.**

1. Epidemiology

As the aging of the population continues to advance, dementia has become an increasingly prominent public health issue. According to relevant studies, dementia affects approximately 6% of the population aged 75 to 79, about 18.3% of those aged 85 to 89, and as high as 41.1% of those over the age of 95 [1] (Figure 1). By 2030, the number of global dementia patients is expected to reach 75 million, and by 2050, this figure is projected to increase to 132 million [2].Vascular dementia (VaD), a clinical syndrome characterized by cognitive decline caused by vascular brain injury due to cerebrovascular lesions and related risk factors, is the second leading cause of dementia after Alzheimer's disease, accounting for 12% to 20% of all dementia etiologies [2]. Vascular cognitive impairment (VCI) encompasses the entire pathological process from vascular mild cognitive impairment (VCIND) to VaD. Among subjects aged 65 to 84, the prevalence of VCIND is higher than that of VaD, and the rate of conversion to dementia as well as mortality rates are significantly increased. The prevalence of VCI increases from 2.0% in the 65 to 74 age group to 13.7% in those over 85 years old. On average, 10% of VCIND patients progress to VaD each year, and approximately 19% of patients progress to VaD after two years [3].

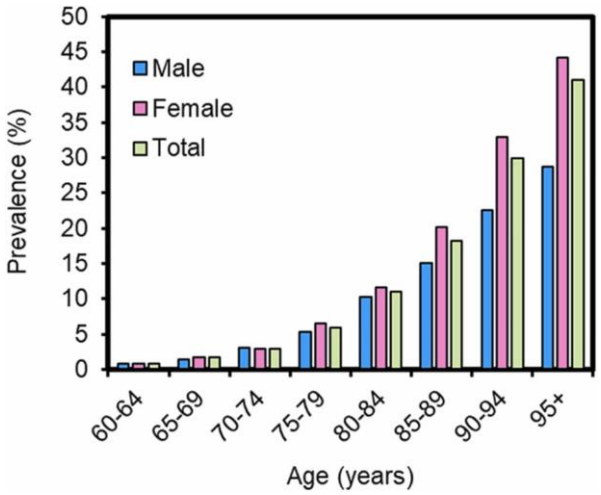

Figure 1: Prevalence of late-onset dementia in the UK by age

2. Definition and Diagnostic Criteria

The definition and terminology of VaD have undergone a continuous evolution since their inception. As early as 1672, Thomas Willis first documented the phenomena of slowed thinking and memory decline in patients after a stroke, which is considered the earliest clinical description of vascular dementia [4]. In 1974, Hachinski and colleagues proposed the concept of multi-infarct dementia (MID) [5]. Subsequently, in 1992, the World Health Organization (WHO) officially unified the nomenclature for vascular dementia in the tenth edition of the International Classification of Diseases (ICD-10). As a diagnostic term, VaD encompasses a variety of clinical and pathological manifestations caused by cerebrovascular diseases, including symptoms of dementia resulting from ischemic stroke, hemorrhagic stroke, and ischemic changes in brain tissue that do not meet the criteria for infarction [6]. Given the limitations of vascular dementia, Hachinski and Bowler et al. proposed the concept of vascular cognitive impairment (VCI) in 1993 [7]. This concept covers the entire disease process from mild to severe vascular cognitive impairment, with VaD becoming a subtype of VCI. In 1999, Sachdev et al. further proposed the concept of vascular cognitive disorder (VCD), which includes VaD and cases of vascular cognitive impairment that do not meet the criteria for dementia (VCIND) [8]. Although the concept of vascular dementia is constantly being refined, its heterogeneity has led to the proposal of different diagnostic criteria. For example, the criteria set by the Alzheimer's Disease Diagnostic and Treatment Center of California (ADDYTC) are limited to ischemic brain injury [9]; ICD-10 requires memory impairment and intellectual decline, affecting the ability to perform daily activities [6]. The NINDS-AIREN criteria define dementia as a decline in cognitive function compared to previous levels, characterized by memory impairment and impairment in two or more cognitive domains. These deficits are significant enough to affect the patient's daily life and are not merely due to physical disabilities caused by stroke [10].

The diagnosis of vascular dementia can take three steps: 1) determining the diagnosis of dementia; 2) judging the degree of dementia; 3) differential diagnosis with other types of

dementia. Regardless of the cause of vascular dementia, the first step in diagnosis must confirm the dementia syndrome. For the diagnosis of vascular dementia, the most basic elements should be as follows: 1) Dementia must be certain; 2) There must be evidence of cerebrovascular disease related to dementia, whether through history, clinical examination, or brain imaging examination to confirm the presence of cerebrovascular disease; 3) The two must be related, except for other causes of dementia. Where VaD is defined as the presence of focal neurological signs consistent with stroke, with or without stroke; sudden or stepped cognitive impairment accompanied by evidence by brain imaging of VaD should be considered as having experienced a stroke [11].

3. Factors Associated with Morbidity

The risk factors for VaD include disease-related and non-disease-related factors. Disease-related factors encompass cerebrovascular diseases, hypertension, atrial fibrillation, type 2 diabetes, elevated low-density lipoprotein, inflammatory diseases, depression, autoimmune diseases, chronic periodontitis, sleep breathing disorders, etc.; while non-disease-related factors involve genetics, aging (especially males over 80), obesity, physical activity, etc. [12-14] Analysis based on big data and computer models indicates that controlling seven key risk factors (obesity, hypertension, diabetes, hypercholesterolemia, smoking, low education level, and cardiovascular diseases) could reduce the number of dementia cases worldwide by one-third, especially VaD. Therefore, controlling vascular risk factors is of significant importance in reducing the incidence of VaD [15].

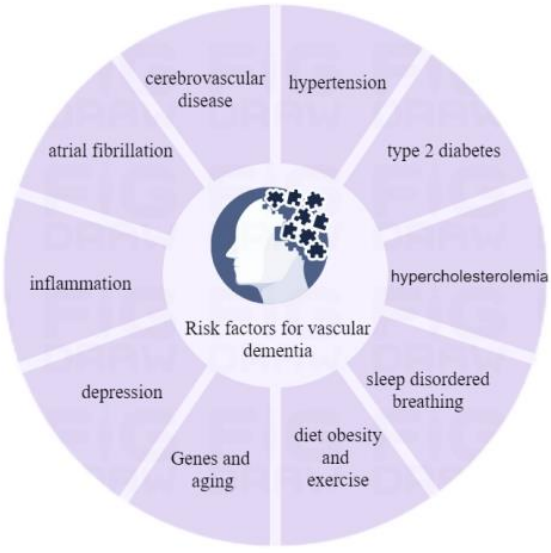

Figure 2: Factors contributing to vascular dementia

4. Pathogenesis

The pathogenesis of VaD is not yet clear, but it is currently believed that the main cause of VaD is vascular lesions. Ischemic stroke is closely related to VaD, and research evidence suggests that 25%-30% of survivors of ischemic stroke will immediately or subsequently develop vascular dementia [16]. The pathological process can be summarized as follows: various risk factors induce cerebrovascular lesions, leading to a reduction in cerebral blood flow. The decrease in cerebral blood flow subsequently causes the disruption of the blood-brain barrier, endothelial dysfunction, and activation of neuroglial cells. These changes collectively contribute to a series of pathological responses including neuroinflammation, oxidative stress, excitotoxicity, and demyelination, ultimately resulting in white matter lesions, synaptic damage, and cerebral atrophy [17-20]. Based on this, VaD is further subdivided into eight subtypes [11]. (See Figure 3.) The currently discovered pathogenesis of VaD mainly includes the cholinergic system theory, excitotoxicity theory, oxidative stress theory, genetic factor theory, inflammatory response, Ca2+ overload, autophagy, cell apoptosis, and the interaction between the neurovascular unit.

4.1 Cholinergic System Disorder

Cholinergic system is related to human cognitive function. As a neurotransmitter of cholinergic system, acetylcholine exists in cholinergic neuron vesicles and is closely related to learning and memory [21]. Under the conditions of ischemia and hypoxia, cholinergic nerves are damaged, resulting in a gradual decrease in the level of pyruvic acid, a decrease in the production of acetyl-CoA in the body, and finally a decline in memory due to insufficient synthesis [22]. An autopsy-based study showed that the loss of cholinergic function was only evident in patients with VaD and concurrent AD [23].

4.2 Oxidative Stress Response and Cell Apoptosis.

Oxidative stress refers to the imbalance of oxidation and antioxidant effects in cerebral ischemia, hypoxia and chronic hypoperfusion, resulting in inflammatory infiltration of neutrophils, production of a large number of lipid peroxidation products and free radicals such as superoxide dismutase (SOD) and malondialdehyde (MDA) brain cells, increasing the number of brain cell necrosis, enlarging the ischemic site, and finally leading to vascular dementia [24]. At the same time, oxidative stress can cause endothelial function and mitochondrial dysfunction and eventually damage the hippocampus, loss of synapses and apoptosis [25].

4.3 Excitotoxicity of Amino Acids and Ca2+ Overload

Excitotoxicity and Ca2+ overload are two interrelated processes. Firstly, during ischemia, the extracellular glutamate concentration significantly increases, activating glutamate receptors and producing excitotoxicity; secondly, because glutamate receptors are dual-gated channels, during ischemia and hypoxia, the activation of N-methyl-D-aspartate (NMDA) receptors on the postsynaptic membrane causes the channels to open, leading to a massive influx of Ca2+, intracellular Ca2+ overload, and resulting in neuronal damage, which in turn leads to vascular dementia [24].

4.4 Inflammation Response Mechanism

After cerebral ischemia, inflammatory responses are induced in brain tissue, and the presence of inflammation further damages cerebral blood vessels, creating a vicious cycle. Following cerebral ischemia, the release of TNF-α and IL-β promotes the endothelium to secrete other inflammatory factors, leading to thickening of the vascular endothelium. Over time, this exacerbates cerebral ischemia, depriving brain

neurons of sufficient nutrients and causing cognitive dysfunction [26-28]. For instance, Bhatia et al. used RT-PCR analysis to study the effect of thromboxane A2 synthase inhibitor Ozagrel in treating VaD patients and found a decrease in the expression of inflammatory cytokines TNF-α and IL-6 [29].

4.5 Genetic Mechanisms

Many rare gene mutations are associated with VaD, and apolipoprotein E (ApoE4) and NOTCH3 are two genes currently identified to be associated with vascular dementia. Among them, familial VaD subtype is most common in CADASIL. Mutations in NOTCH3 gene can lead to autosomal dominant subcortical infarction and leukoencephalopathy [30]; ApoE4 affects the metabolic level of blood lipids, among which ApoE4 increases total cholesterol and low-density lipoprotein, and the appearance of arteriosclerosis accelerates the appearance of vascular dementia [31].

Table 1: Classification of Vascular Dementia

somatotype	reason
Small vessels disease (SVD) /Binswanger's disease	Sub-cortical infarcts (HTN/DM)
Hypoperfusion dementia	Cortical infarct, large artery occlusion (atherothrombotic or cardioembolic)
The critical position of the infarction	Thalamus, caudate, hippocampus and genu of internal capsule
Hypoperfusion dementia	Water shed infarct/ orthostatic hypotension and variation in blood pressure
Mixed dementia	Vascular disease along with Alzheimer disease or Dementia of leiw body
Hemorrhagic	Micro-bleed, CAA (APP codon 693 mutation)
Hereditary vascular dementia	CADASIL (NOTCH 3 gene mutation) and CARASIL (mutation in HtrA serine protease gene)
Vascular dementia/Vascular cognitive impairment/post-stroke dementia	All of the above causes

5. Emerging Perspectives

5.1 Gut Microbiota

The human gut microbiota, the enteric nervous system, the immune system, and the central nervous system together form a complex signaling network known as the gut-brain axis. Within this axis, the gut microbiota plays a key role in information transmission [32]. When the gut microbiota is imbalanced, on one hand, it can excessively produce harmful metabolites such as lipopolysaccharides and immunogenic substances. These substances can damage the blood-brain barrier, trigger inflammatory responses in the central nervous system, lead to apoptosis of brain cells, and thereby affect a person's mood, cognition, and behavior. On the other hand, the gut microbiota indirectly affects brain function through various pathways, including the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, the immune system, and the endocrine system, and is involved in the pathogenesis of VaD [33,34]. Studies have shown that regulating the gut microbiota can improve cognitive function in patients with VaD [35]. Under pathological conditions, stress-induced damage to the intestinal mucosal barrier and dysbiosis of themicrobiota can lead to increased permeability of the blood-brain barrier, making various gut pathogens and inflammatory factors more likely to enter the central nervous system through the gut-brain axis and the circulatory system. This can trigger neuroinflammatory responses in areas such as the cerebral cortex and hippocampus, resulting in cognitive dysfunction and behavioral abnormalities [36].

5.2 Epigenetics

Epigenetics, aging, and VaD, as well as the factors related to VaD pathogenesis (such as cerebrovascular diseases, hypertension, diabetes, depression, etc.), are closely interconnected. Within the scope of epigenetic research, DNA methylation is currently one of the most focused areas of study [37]. The hippocampus serves as the pathological basis of dementia, and its tissue atrophy is a prominent feature of subcortical VaD [38], making it a core content of epigenetic research. In a study on the hippocampus of VaD rats [39], researchers revealed hypomethylation of the vascular endothelial growth factor (VEGF) and kinase insert domain-containing receptor (KDR) genes.

MicroRNAs (miRNAs) are a class of non-coding RNA molecules that regulate gene expression at the post-transcriptional level. Numerous studies have confirmed that miRNAs can serve as novel clinical biomarkers and potential therapeutic targets for VaD [40,41]. For instance, studies have indicated that regulating the miR-193b-3p/CaM and miR-152-3p/CaMKIIα-mediated inflammatory and apoptotic pathways can effectively ameliorate cognitive decline in VaD patients [42,43]. Additionally, miR-409-3p, miR-502-3p, miR-486-5p, and miR-451a have also been proposed as potential biomarkers for VaD [43,44].

Histone modifications are also crucial in the transformation of the epigenetic landscape during aging [45]. Histone deacetylase (HDAC) catalyzes histone deacetylation, which may represent a potential therapeutic target for VaD [46]. In one study, when donepezil was used to treat a VaD rat model, a reduction in nuclear translocation of HDAC6 was observed, along with a decrease in its binding to promoter IV of the brain-derived neurotrophic factor (BDNF) gene in the cortex [47].

6. Treatment

The treatment for VaD includes non-pharmacological interventions, pharmacological therapy, and rehabilitation training. Non-pharmacological interventions mainly involve dietary adjustments and physical exercise. Numerous studies have shown that consuming omega-3 fatty acids and following a Mediterranean diet can prevent cognitive decline [37]. Progressive aerobic exercise training has been proven to reduce the risk of post-stroke vascular dementia (PSD) and improve cognitive function [48]. VPharmacological treatment for VaD involves cholinesterase inhibitors such as donepezil, galantamine, and rivastigmine. According to AHA/ASA recommendations and recent meta-analyses, donepezil and rivastigmine have been particularly effective in improving cognitive function [48,49]. Other medications, such as the NMDA receptor antagonist memantine [50], the antioxidant drug edaravone [51], and the calcium channel blocker

nimodipine [52], have also been shown to improve cognitive status. It is crucial to control risk factors associated with VaD. Statins help lower cholesterol, anti-thrombotic and anticoagulant drugs are used to treat cardioembolic stroke or transient ischemic attacks, and blood pressure-lowering drugs and edaravone, which scavenges free radicals, are key pharmacological strategies. In addition, emerging drugs such as the γ-aminobutyric acid derivative oxiracetam, synthetic phosphatidylcholine cytidine diphosphate choline, and cerebrolysin extracted from pig brains are important components of VaD treatment [53,54]. However, it is not to be overlooked that rehabilitation training can also significantly improve the cognitive function of patients. Numerous studies have confirmed that participating in cognitive rehabilitation training courses can effectively enhance the cognitive abilities of patients [55].

7. Prospect

In summary, to date, there is no unified consensus or comprehensive description regarding the pathogenesis of vascular cognitive impairment. Further in-depth research is still needed on the etiology, clinical manifestations, and treatment strategies of VaD. Especially for mild VaD, early identification of its risk factors and formulation of corresponding diagnostic and treatment plans are crucial to prevent or delay the progression of vascular cognitive impairment, no dementia (VCIND) to dementia, thereby blocking the occurrence of VaD as much as possible.

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