Progression in Vascular Cognitive Impairment: Pathogenesis, Neuroimaging Evaluation, and Treatment

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Abstract

Vascular cognitive impairment (VCI) defines an entire spectrum of neurologic disorders from mild cognitive impairment to dementia caused by cerebral vascular disease. The pathogenesis of VCI includes ischemic factors (e.g., large vessel occlusion and small vessel dysfunction); hemorrhagic factors (e.g., intracerebral hemorrhage and subarachnoid hemorrhage); and other factors (combined with Alzheimer's disease). Clinical evaluations of VCI mainly refer to neuropsychological testing and imaging assessments, including structural and functional neuroimaging, with different advantages. At present, the main treatment for VCI focuses on neurological protection, cerebral blood flow reconstruction, and neurological rehabilitation, such as pharmacological treatment, revascularization, and cognitive training. In this review, we discuss the pathogenesis, neuroimaging evaluation, and treatment of VCI.

Keywords

vascular cognitive impairment, pathogenesis, neuroimaging, treatment, progression

Vascular cognitive impairment (VCI) is a syndrome that includes all cognitive disorders attributable to various kinds of cerebral vascular disease and relative risk factors, and it is generally used to capture the entire spectrum of neurologic disorders, ranging from mild to severe[1]. It usually affects advanced brain functions, especially executive function and memory[2]. Although the definition and diagnostic criteria of VCI remain disputed, VCI can be classified by its clinical characteristics as vascular mild cognitive impairment, vascular dementia, and mixed dementia (MD) associated with vascular dysfunction, whose risk factors include age, hypertension, hyperlipidemia, hyperuricemia, diabetes, cardiopathy, stroke, carotid plaque, smoking, and low educational level[3,4]. Recent studies of VCI have mainly focused on its pathogenesis, evaluation, and treatment, and the present study aimed to summarize these advances.

Pathogenesis

The pathogenesis of VCI can be attributed to ischemic factors, hemorrhagic factors, and other factors affecting functional brain regions[5,6]. On this basis, atrophy of the gray matter and hemispheric white matter lesions caused by cerebral vascular diseases (CVD) becomes the main structural change of VCI[7–9]. Relating to these pathophysiological changes, many studies have provided new insight[10,11].

Ischemic Factors

Large Vessel Occlusion. The occlusion of large vessels, such as ischemic stroke caused by cardio embolic and atherosclerotic diseases, constitutes a large brain infarct[5]. Many findings and the TABASCO study have confirmed that inflammatory mediators play an important role, together with amyloid deposition, in the development of VCI after stroke[12]. Back et al.[13] reported that the occlusion of a large vessel may

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interfere with amyloid clearance through the glymphatic pathway and concomitant neuroinflammation to form VCI. Relevant results have suggested that cognitive decline appears, on average, after 2 years because of long-lasting effects on remote white matter integrity[8]. In particular, Mandzia et al.[14] found that changes in executive function and psychomotor processing speed appear within 90 d after stroke.

Small Vessel Dysfunction. The dysfunction of small vessels supplying important brain regions, such as arteriosclerosis and arteritis, can cause cortical and subcortical microinfarcts[15], which result in long-time hypoperfusion because of decompensation of collateral circulation, and which appear to be the most robust substrates of cognitive dysfunction[16,17]. In particular, some findings[18] on hereditary diseases, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), have provided new insight into the mechanisms of dementia associated with cerebral small vessel disease. Rosenberg[19] found that cerebral hypoperfusion leads to fibrosis of the extracellular matrix and activates neuroinflammation, which is most damaging to the deep white matter. These types of multiple infarctions and diffuse white matter lesions often appear in the lateral ventricle and subcortex, resulting in multicognitive domain impairment.

Hemorrhagic Factors

Intracerebral Hemorrhage. Patients have significant cognitive impairment after intracranial hemorrhage (ICH)[20,21]. Visual-processing functions decline obviously in this type[22,23]. Many studies[22,24–27] on intracranial microbleeds have confirmed that cerebrovascular amyloidosis contributes to dementia and cognitive impairment by means of worsening vascular amyloid-β accumulation, activation of vascular injury pathways, and impaired vascular physiology[6], while others[28] indicate that the disturbance of brain iron metabolism after ICH caused by inflammation can also enhance brain injury and contribute to VCI.

Subarachnoid Hemorrhage. Cognitive dysfunction commonly appears with subarachnoid hemorrhage (SAH)[29]. The anterior cingulate gyrus and frontobasal regions are often involved in SAH, resulting in neurocognitive deficits including visuospatial memory and language[30]. A recent study[31] showed that the left parahippocampal gyrus, left inferior temporal gyrus, and left thalamus are also involved in the formation of VCI in patients with SAH. New findings[32] established that the pathogenesis of VCI may be attributed to the impact of the subdural membrane on dural lymphatics. This mechanism, however, is still controversial, and relevant research is needed.

Other Factors

VCI can appear in the condition of CVD combined with Alzheimer's disease (AD), which often results from both vascular disorders and structural changes in protein in brain tissue[1]. Apart from the increased levels of tau protein in cerebrospinal fluid among patients with VCI, Kalaria[33] believes that there is a vascular basis for neuronal atrophy in MD entirely independent of AD pathology, which often appears with memory decline[34].

Evaluations

Clinical Evaluation

The diagnosis of VCI relies on wide-ranging clinical evaluations, including pathological confirmation, neuropsychological tests, and multi-modal neuroimaging measures[35]. When lacking the appropriate brain samples for pathological diagnosis, Skrobot et al.[36] suggest using neuropsychological and imaging assessments for the diagnosis of VCI. However, there are no specific neuropsychological tests for patients with VCI[37]. Neuropsychological testing is easy to do in the clinic, although, due to self-limitations such as ceiling effects, floor effects, and subjective influence[38–40], only neuroimaging has been relevant for clinical practice regarding the differential diagnosis of dementia[41].

Neuroimaging

Structural Neuroimaging. Structural changes in the brain have tight connections with VCI, which can be detected on structural magnetic resonance imaging (sMRI)[42]. Some studies[7,43] suggest that different sequences of MRI can make contributions to the objective evidence of latent VCI, such as cortical lesions and significant gray matter atrophy. By means of using dynamic contrast enhanced MRI, Raja et al.[44] found a new mechanism of VCI as dysfunction of the blood–brain barrier. However, routine MRI has low sensitivity to brain microstructural changes, which are common in VCI. Suri et al.[45] determined the association of intracranial atherosclerotic stenosis and cognitive dysfunction with the evidence of white matter hyperintensity and vascular change using 3.0 T time-of-flight MRI. In addition, the application of high-field MRI can provide high resolution to the evidence of VCI, such as changes in the cerebral perivascular spaces[46].

Other sequences of MRI, such as diffusion tensor imaging (DTI) in animals, suggest the structural damage of white matter can become a biomarker of VCI[47], which is also confirmed with the evidence of white matter connective dysfunction. Fragata et al.[48] suggested that DTI parameters can make contributions to the monitoring of delayed cerebral ischemia at early stages of post-SAH, which is independently associated with functional outcome and can be a prognosis in SAH-related VCI. Williams et al.[49] used a segmentation technique to predict white matter microstructural damage as a surrogate marker of VCI.

Hemorrhagic factors related to VCI, however, may produce obvious structural changes, while ischemic factors, such as hypoperfusion, may result in VCI with functional
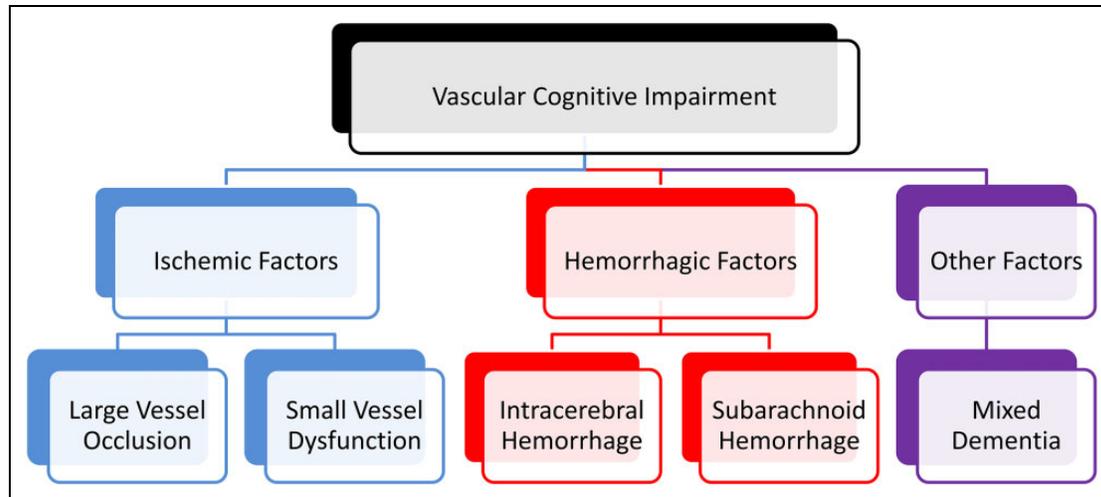
Fig. 1. Various pathogenic factors of VCI. From the angle of pathogenic factors, VCI can be classified into three subtypes. The ischemic type includes large vessel occlusion and small vessel dysfunction. The hemorrhagic type often refers to all kinds of intracranial hemorrhage as well as subarachnoid hemorrhage. In addition, AD can often appear along with vascular disorder to form mixed dementia.

changes at first[50]. Such differences should be differentiated and clarified.

Functional Neuroimaging. Cerebral hemodynamic perfusion, such as single photon emission computed tomography (SPECT) and positron emission computed tomography (PET), can evaluate the level of brain metabolism and blood perfusion to reflect brain function and provide evidence of VCI[6]. Ishikawa et al.[51] reported that cognitive dysfunction has a correlation with cerebral perfusion. Although it has been confirmed that mild cognitive impairment is tightly related to cerebral glucose hypometabolism, the relevance of cerebral metabolism to VCI is still not clear[52].

As a burgeoning, noninvasive examination with high spatial sensibility, functional MRI (fMRI) has become an efficient method to assess neural function based on the principle of contrast enhancement of blood oxygen level dependence (BOLD), which measures the neuron activity related to hemodynamic changes in various brain regions[53]. fMRI provides us a chance to understand the pathogenesis of VCI from neural, regional, and network levels[54]. At the regional level, Diciotti et al.[55] noted that high regional homogeneity in the left posterior cerebellum and middle cingulate cortex indicates global cognitive impairment and worse executive functions. At the network level, Lei et al.[56] found that the default mode network and executive-control network can influence executive performance for patients with VCI by means of analyzing the amplitude of low-frequency fluctuations in the dorsolateral prefrontal cortex and posterior cingulate cortex. fMRI is a measurement of high spatial resolution but low temporal resolution, thus other measurements with high temporal resolution are needed.

Electroencephalogram (EEG), which can reflect the overall electrophysiological effect and the function of the brain network, is a noninvasive, time-focused information transmission and processing method with high temporal resolution that uses nonlinear dynamic analysis and time frequency analysis to reflect the dynamic time processing of information transmission accurately[57]. Moretti et al.[52] found that patients with cognitive impairment show abnormal activation in the H-alpha/L-alpha power ratio compared with normal persons, as a clinical biomarker, indicating the adaptation in these brain region changes. With the progression of cognitive dysfunction, the degree of abnormal EEG is also aggravated, especially in event-related potentials, which indicates that EEG can be used as a reliable objective index for evaluating the severity of cognitive impairment[58]. The application of EEG in brain default networks provides new insight into the mechanism of cognitive impairment, while related research on VCI by means of EEG is still poor. Some limitations of EEG also restrict the use of this technique to only detect the neuronal activity of the cortex, and it is easily affected by the skull. Some deep neuronal activity can hardly be observed with existing devices, which suggests that new methods need to be developed[59,60] (Fig. 2).

Functional near-infrared spectroscopy (fNIRS) has been used as a new monitoring method to reflect the level of advanced cognition. It has the advantage to reflect neural mechanisms in natural situation from special tasks in the cognitive evaluation[61]. Beishon et al.[62] used fNIRS to evaluate brain hemodynamics and oxygen metabolism to predict cognitive decline at an early stage. Similar to EEG, magnetoencephalography (MEG) is another new method to detect deeper comprehension of brain dynamics with fewer conduction effects and higher temporal resolution compared with EEG[63]. Using MEG, Baillet[64] concluded the mechanisms of functional connectivity between regions and the emergence of modes of network communication in brain systems.
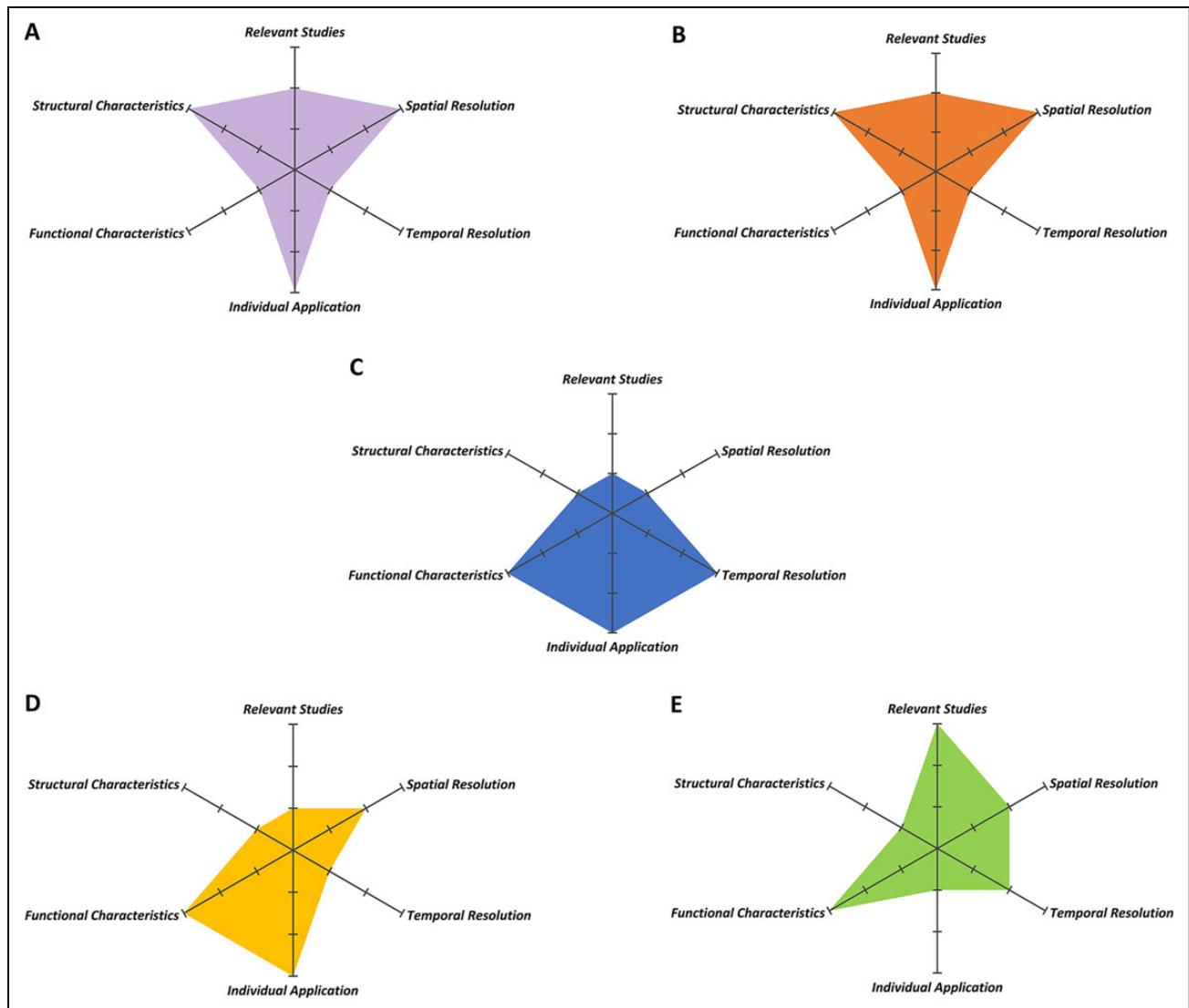
Fig. 2. Various kinds of neuroimaging in the evaluation of VCI. Different kinds of neuroimaging (A. Gray matter volume, B. DTI, C. EEG, D. PET/SPECT, E. fMRI) in the contributions of VCI are summarized from six dimensionalities including the evidence from relevant studies and individual application in diagnosis for VCI (Relevant Studies, Individual Application), spatial and temporal resolution (Spatial Resolution, Temporal Resolution), and functional and structural characteristics of each neuroimaging (Functional Characteristics, Structural Characteristics). Each dimensionality is divided into three levels of excellent, medium, or lacking. The superior and inferior kinds of neuroimaging are shown below.

Treatment

Medical Treatment

VCI and AD often coexist and share clinical features and multiple neurotransmission involvement. According to the mechanism of cognitive impairment, acetylcholinesterase inhibitors, such as donepezil and rivastigmine, have been proven to decrease the amyloid beta deposition in the development of AD in mouse models[65]. Excitatory amino acid receptor antagonists, such as memantine, are another pharmacotherapy for cognitive impairment that have been confirmed in the clinic. Recently, various new drugs have been explored for the treatment of cognitive impairment. Guekht

et al.[66] reported that actovegin has been tested for post-stroke cognitive impairment in clinical trials. Some drugs used in the treatment of cognitive dysfunction, such as donepezil and galantamine, have been generally accepted to treat AD and approved for modest cognitive benefits for VCI in the clinic[67]. More evidence and related research are still needed to confirm efficiency.

Revascularization

According to the pathogenesis of VCI, increasing regional cerebral blood flow by means of revascularization is hypothesized to improve cognition[68,69]. Lattanzi et al.[70]

showed that cognitive performance can be improved with the development of cerebral vasomotor reactivity after carotid endarterectomy. Carotid artery stenting is another method used to improve cerebral perfusion that is also reported, using fMRI, to partly improve global cognition and memory, resulting from the increased perfusion in the left frontal gyrus and amplitude of low-frequency fluctuation in the right precentral gyrus connectivity to the posterior cingulate cortex in the right supra frontal gyrus[71]. Noshiro et al.[72] confirmed the improvement of brain networks by means of neuroimaging after bypass surgery in moyamoya disease. With the accumulating evidence, it is generally accepted that the cerebrovascular reserve may be related to cognition[51], which provides a potential method for the surgical treatment of VCI.

In contrast, some studies have shown that there is no significant improvement of cognitive level after revascularization[73]. Turan et al.[74] argued that angioplasty and stenting showed no improvement in cognitive impairment compared with medical treatment alone during follow-up. The RECON trial[75] showed cognitive improvement following bypass surgery was not superior to medical therapy. The inconsistent results across different studies may be attributed to the different evaluating standards and methods, and more studies and randomized clinical trials are needed to confirm the efficiency of surgical treatment.

Neurological Rehabilitation

Although neuroprotection and neurorecovery enhancement have become important methods for treating VCI, studies regarding neurological rehabilitation are also faced with the difficulty of establishing a standard protocol that can embrace a holistic approach in cognitively impaired patients[76]. Perng et al.[77] performed a meta-analysis and found that symptomatic cognitive training is an effective intervention for VCI. Ahn et al.[78] also suggested that long-term treadmill exercise can restore memory function through replacement of multiple damaged structures in the ischemic aged hippocampus, and indicated that long-term exercise begun after ischemic neuronal death as a chronic neurorestorative strategy is efficient.

Transcranial magnetic stimulation (TMS) was first used in cerebrovascular disease to identify a pattern of cortical hyperexcitability, which is caused by a disruption in the integrity of white matter[79]; however, in VCI, the application of TMS points to enhancing brain cortical excitability and synaptic plasticity, indicating its potential to become an innovative rehabilitative tool to restore impaired neural plasticity and provide further understanding of neurotransmission pathways and plastic remodeling in the pathogenesis of VCI[80]. More relative research is needed to confirm the efficiency and safety of TMS to find more alternative methods for the neurological rehabilitation of VCI.

Conclusion and Future Direction

In conclusion, the pathogenesis, neuroimaging evaluation, and treatment of VCI have made a lot of progress. However, there is still scope for further exploration of the mechanism, especially in the field of correlation between molecular biology and multi-model neuroimaging, and there is great potential for the early identification and diagnosis of VCI. Meanwhile, more evidence about medical treatment in VCI is needed. The safety and efficiency of neurological rehabilitation should also be confirmed. The combination of pharmacotherapy, revascularization, and rehabilitation may become a main therapeutic method for VCI in the future.

Author Contribution

Xin Zhang and Jiabin Su, equal contribution on this work as the first authors.

Declaration of Conflicting Interests

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