Cognitive Impairment in Patients with Stroke

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Abstract

Despite substantial advances in stroke care, vascular cognitive impairment remains a prominent source of disability. Unlike sensorimotor impairments, cognition often continues to decline after stroke. An aging population will increase the prevalence of vascular cognitive impairment, with stroke playing an important role. Ten percent of patients presenting with stroke have pre-stroke dementia; an additional 10% will develop incident dementia with a first stroke, and 30% with a recurrent stroke. While stroke increases the risk of cognitive impairment, the presence of cognitive impairment also impacts acute stroke treatment and increases risk of poor outcome by nearly twofold. There is substantial overlap in the clinical and pathological aspects of vascular and degenerative dementias in many patients. How they relate to one another is controversial. The treatment of vascular cognitive impairment remains supportive, focusing on treating vascular risk factors. Cognitive rehabilitation after stroke is an area of active research, and existing pharmacologic treatments have limited benefit. Heightened awareness of cognitive impairment in the setting of stroke is imperative for prognostication and management, impetus for research and, ultimately, the discovery of efficacious treatments.

Keywords

- stroke
- cognitive impairment
- dementia
- imaging
- biomarkers
- cerebrovascular disease

Approximately 50 million people are living with dementia worldwide, a number expected to reach 82 million by 2050.[1] *Vascular dementia* (VaD) is the second most prevalent cause of dementia after Alzheimer's disease (AD), comprising ~15% of cases.[2] The term *vascular cognitive impairment* (VCI) encompasses a spectrum from mild cognitive dysfunction to dementia in the setting of cerebrovascular disease. Although difficult to estimate reliably because of variability in diagnostic thresholds and nosology, the contribution of cerebrovascular disease to the global burden of cognitive impairment is becoming more apparent. The prevalence of VaD doubles about every 5.3 years.[3] Historically regarded as a distinct form of dementia, most cases of dementia are mixed with features of both cerebrovascular disease and AD.[4] While coexisting cerebrovascular disease decreases the threshold for the clinical expression of dementia in the setting of neurodegenerative disease,[5] it remains unclear if cerebrovascular disease is additive with AD pathology in causing cognitive impairment, or synergistic such that it increases the hallmark pathologies of AD (amyloid plaques and neurofibrillary tangles). Mechanisms by which cerebrovascular disease may accelerate neurodegeneration have been speculated. For instance, oxidative stress, endothelial dysfunction, increased blood–brain barrier permeability, cerebral blood flow dysregulation, inflammation, trophic uncoupling of the neurovascular unit, and demyelination are features of vascular pathways associated with neurodegeneration.[6] Radiographic and pathologic studies have shown that most neurodegenerative dementias beyond AD also have coincident cerebrovascular disease.[7] A meta-analysis including participants with and without dementia demonstrated that vascular-type pathology and mixed vascular–AD pathology were both likely to be found in patients with dementia, and that patients with mixed pathology had almost twice the risk of dementia compared with patients with pure

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AD pathology.[8] Cerebrovascular disease, however, is common in populations >65 years; 30% have silent infarcts and 90% have white matter disease.[2] It is difficult to ascertain the contribution of vascular pathology to cognitive decline from observational studies alone[2]; however, the common coexistence of cerebrovascular disease and cognitive impairment is undeniable.

The complexity of the relationships among cerebrovascular disease, neurodegeneration and cognitive impairment increases in the presence of clinical stroke. Stroke doubles the risk of developing dementia,[9] and rates of cognitive decline in those with cognitive impairment significantly increase after ischemic stroke.[10] Recurrent stroke more than doubles the risk for post-stroke dementia.[11] Dementia, in turn, is associated with an increased risk of stroke.[12] Both dementia and stroke are significant sources of mortality,[13,14] have enormous societal implications,[15,16] and remain priorities in research. A comprehensive understanding of the mechanisms leading to VCI and its interaction with neurodegeneration are imperative to identify potential preventative strategies and treatments. The purpose of this review is to address the epidemiologic, diagnostic and therapeutic aspects of cognitive impairment and dementia in patients with stroke.

Definitions of Vascular Cognitive Disorders

The terminology and diagnostic criteria for the spectrum of vascular cognitive disorders (VCD) has varied over the years. Consensus on the criteria for VCD has been difficult to achieve due to the broad continuum of pathophysiology and clinical manifestations of cerebrovascular disease. "Senile dementia" was considered a result of cerebral atherosclerosis through the 1960s,[2] until studies established AD as the main contributor to dementia.[17] Later, VaD was thought to be limited to cases involving multiple large cerebral infarcts, which were diagnosed as *multi-infarct dementia*.[18] With advances in neuroimaging and the publication of large pathological studies, it became apparent that the VCD involve a spectrum of diseases of large and small vessels, leading to updated criteria.[19–21]

There have been several proposed terms for cognitive disorders in the setting of cerebrovascular disease.[2,3,20,22] VCI is a term recently used by the Vascular Impairment of Cognition Classification Consensus Study (VICCCS) to describe this spectrum of diseases[22,23] (►**Fig. 1**). According to VICCCS, VCI is classified into mild and major subtypes. The mild subtype includes cognitive impairment in a single domain, whereas the major subtype additionally requires significant effects on daily functioning. The major forms of VCI, which encompass *VaD*, are subcategorized based on underlying mechanism into *post-stroke dementia*, *subcortical ischemic VaD*, *multi-infarct (cortical) dementia,* and *mixed dementia*. "Post-stroke dementia" has been proposed to describe cognitive impairment that has a clear onset within 6 months after a stroke.[22,23] Despite improvements, the inclination to attribute cerebrovascular disease as the exclusive cause of cognitive impairment in a particular individual remains a limitation of current classification schemes.

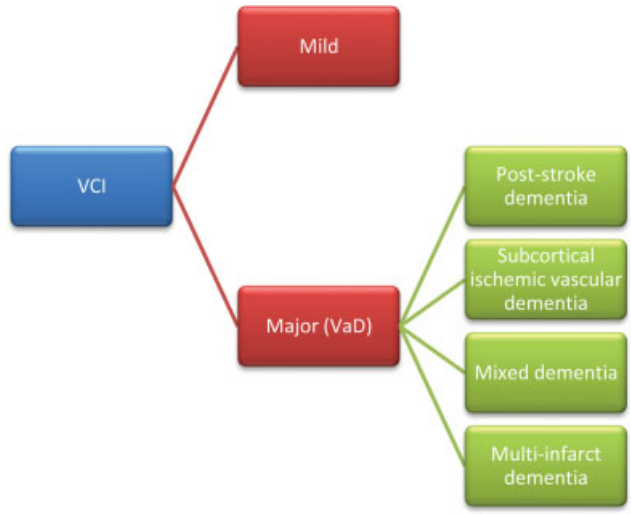

Fig. 1 Vascular Impairment of Cognition Classification Consensus Study (VICCCS) conceptualization of vascular cognitive impairment. VaD, Vascular Dementia; VCI, vascular cognitive impairment.

Cognitive Impairment in the Setting of Stroke

The prevalence of dementia at the time of stroke is ~8 to 14%.[24–27] The rate of dementia prior to stroke is about half of the rate after stroke, and about one-third of the rate after recurrent stroke.[26] Severe stroke can increase the dementia risk up to 50 times compared with the general population.[27] Independent of vascular risk factors for every decreased standard deviation of cognitive performance, there is a 15% higher risk of stroke.[25] In addition to shared risk factors, cognitive impairment may increase the risk of stroke by being an expression of microvascular disease, which may later progress to clinical stroke.[28]

Implications for Acute Stroke Care

Dementia prior to stroke independently predicts neurologic deterioration during the acute phase of stroke. Altered cerebrovascular hemodynamics may have a role.[24] Cerebrovascular autoregulation and vasomotor reactivity are significantly impaired in patients with dementia.[29,30] Cognitive impairment is not considered an exclusion criterion for thrombolysis in evidence-based guidelines of acute ischemic stroke care.[31] However, individualized decision-making based on life expectancy and premorbid functional status is recommended.[31] Rates of treatment with thrombolytic agents are lower in patients with acute stroke and dementia compared with acute stroke overall.[32] Dementia is a source of concern in the setting of acute stroke treatment, as up to 24% of patients with AD dementia have cerebral microbleeds on hemosiderin-sensitive magnetic resonance imaging (MRI) sequences.[33] A meta-analysis of 2,208 patients showed that the risk of post-thrombolytic symptomatic intracerebral hemorrhage (ICH) increases as the number of cerebral microbleeds increases.[34] In another study, ICH after thrombolysis ranged from 1.2% in patients without cerebral microbleeds to 30% in patients with ≥ 5 microbleeds.[35] Regardless, no randomized control trial has included baseline MRI assessment of microbleeds; therefore, having microbleeds

does not completely preclude thrombolysis, but cases should be considered on an individual basis.[36] In addition to increasing the risk of hemorrhage, having multiple cerebral microbleeds is also associated with cognitive decline.[37]

The safety and efficacy of acute endovascular treatment in patients with dementia are not known, as participants in randomized trials were excluded for poor premorbid functional status or comorbid neurologic disease.[38–40] An analysis of the MR CLEAN Registry, however, showed that in patients with pre-stroke dependence (defined as modified Rankin Scale [mRS] 3 to 5), a favorable outcome (defined as no worsening of mRS) was seen in only 27% compared with 42% of pre-stroke independent (mRS $\leq$2) patients.[41]

Outcomes in Patients with Pre-existing Dementia and Stroke

Dementia is independently associated with in-hospital mortality and poor 3-month functional outcomes after stroke.[24,42] Rates of pre-stroke dementia are higher in patients with more severe strokes.[27] Patients with dementia are less likely to receive intensive rehabilitation compared with patients without dementia after stroke.[43] This disparity may relate to bias that premorbid cognitive impairment negatively affects rehabilitation potential; however, there is no convincing evidence for this. A retrospective study found that pre-stroke dementia did not alter motor gains in the post-acute period.[44]

Post-Stroke Cognitive Impairment

The reported prevalence of post-stroke dementia varies considerably due to heterogeneity of diagnostic criteria,[45,46] study design, and heterogeneity of study populations.[11] Baseline independent predictors (►**Table 1**) of post-stroke dementia include older age, lower education, cognitive status, pre-morbid dependency, prior stroke, diabetes mellitus, and atrial fibrillation.[11,27] Atrial fibrillation has been shown by numerous studies to be associated with cognitive decline, even in the absence of stroke. Proposed mechanisms of this relationship include silent infarcts, microhemorrhages, hypoperfusion, and inflammation.[47]

Stroke characteristics (i.e., larger infarct volume, stroke severity, presence of aphasia, stroke location, hemorrhagic stroke, multiple infarcts) and early stroke complications (i.e., incontinence, seizures, acute confusion, hypoxia and hypotension) significantly influence the development of post-stroke cognitive impairment.[11] Patients with recurrent clinical stroke have about three times the rate of dementia as those with first stroke,[25] and accordingly radiographic evidence of previous cerebral infarction is predictive of cognitive performance in stroke.[48,49] The incidence of dementia after stroke depends heavily on the clinical severity of stroke, as patients with an National Institute of Health Stroke Scale (NIHSS) >10 had rates >30% at 1 year.[27]

Biomarkers of Post-Stroke Cognitive Impairment

Baseline Imaging Biomarkers (►Fig. 2a)

Subcortical white matter disease, cortical atrophy, and medial temporal lobe atrophy (►**Figs. 2b** [A, D, H]) are all well-established substrates for post-stroke cognitive impairment.[25,26,50–54] Several measures have been used to characterize cerebrovascular disease burden: white matter hyperintensities, cerebral microbleeds, lacunar infarctions, dilated perivascular spaces, acute cortical infarctions, large vessel stenosis, global cortical atrophy, and superficial siderosis[55] (►**Fig. 2b** [A, G, B, F]). Most of these represent markers of small vessel disease (SVD), which is thought to be one of the most important contributors to VaD.[3,56] For example, a systematic review assessing cognitive impairment after lacunar stroke reported prevalence of dementia after lacunar stroke at 20%.[57] While cognitive domains of attention/working memory and executive function are often affected by lacunar infarcts, global cognition and other domains including memory, language, and visuospatial function can be affected as well.[58] Additionally, enlarged perivascular spaces in the basal ganglia may be associated with cognitive impairment after 1 year.[59]

One recently created index, the SVD score, assigns one point for each of the following characteristics: $\geq$1 lacune, $\geq$1 microbleed, moderate-to-severe perivascular spaces in basal ganglia, and white matter hyperintensities (periventricular Fazekas grade 3 or deep Fazekas grade 2 or 3).[60,61] Fazekas scores are typically scored based on findings on fluid-attenuated inversion recovery (FLAIR) imaging. Periventricular Fazekas grade 3 white matter hyperintensities would be are irregular periventricular hyperintensities extending into the deep white matter. Deep white matter hyperintensities are

Table 1 Baseline and index stroke characteristics and biomarkers of small vessel disease that increase risk of post-stroke cognitive impairment

Baseline characteristics	Stroke characteristics	Biomarkers of small vessel disease
History of prior stroke	Size of stroke	White matter hyperintensities
Age	Stroke severity (i.e., NIHSS >10)	Cerebral microbleeds
Lower education	Stroke location (thalamus, angular gyrus, hippocampus)	Dilated perivascular spaces
Premorbid dependency	Hemorrhage	Superficial siderosis
Diabetes mellitus	Stroke related complications (i.e., incontinence, seizures, delirium, hypoxia, hypotension)	
Atrial fibrillation	Lacunar infarct	

Abbreviation: NIHSS, National Institute of Health Stroke Scale.

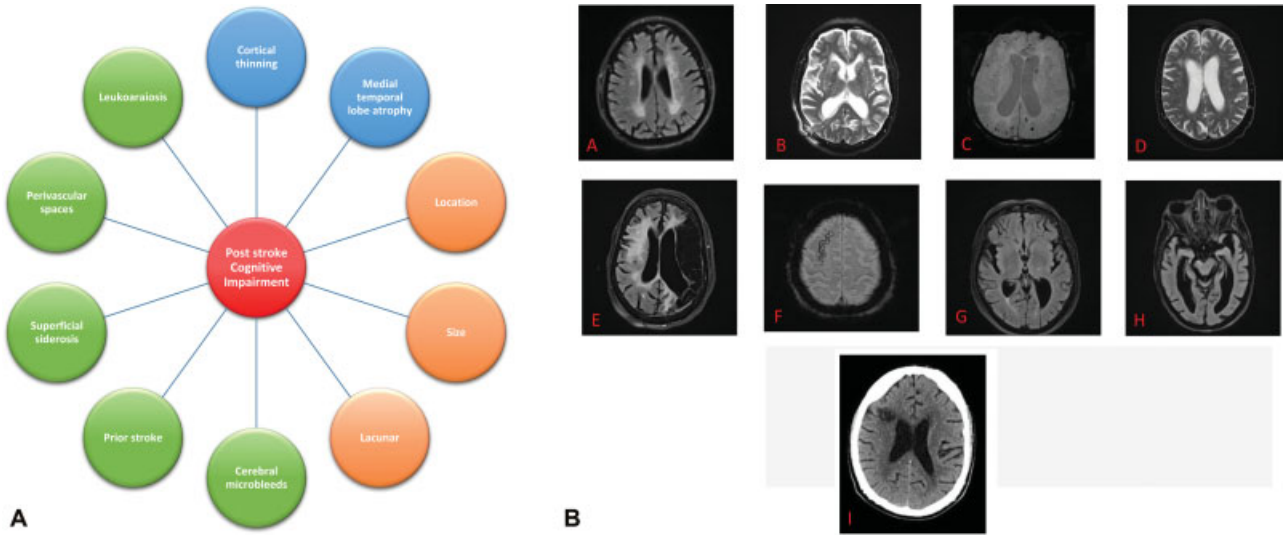

Fig. 2 (a) Imaging features associated with post-stroke cognitive improvement. (Blue: Baseline structural risk factors, Orange: intrinsic qualities of stroke, Green: markers of small vessel disease). (b) Imaging features associated with post-stroke cognitive improvement. (A) Leukoaraiosis, (B) perivascular spaces, (C) cerebral microbleeds in a patient with cerebral amyloid angiopathy, (D) cortical thinning, (E) chronic large right and left hemisphere ischemic infarctions, (F) focal right frontal superficial siderosis, (G) chronic left thalamic ischemic infarction, (H) left > right medial temporal lobe atrophy, (I) chronic right frontal ischemic infarction.

scored as Fazekas grade 2 if there are the beginnings of confluent foci or grade 3 if more extensive confluent foci. These characteristics are included in the Standards of Reporting Vascular Changes on Neuroimaging (STRIVE), which also includes brain atrophy among the neuroimaging features of SVD.[62] Clinically, these lesions are best identified on MRI, specifically diffusion-weighted imaging, T1-weighted, T2-weighted, gradient echo or susceptibility-weighted imaging, and FLAIR sequences.[62] The clinical utility of the SVD score after acute stroke to predict cognitive impairment is still contested, and more advanced imaging techniques, such as diffusion tensor imaging, may be more predictive of cognitive status.[63] Ordinal metrics like the SVD score have many limitations as biomarkers for cognitive impairment, specifically as measures such as cerebral microbleeds appear to have a dose effect, meaning the effect on cognition is more pronounced with increase in number of lesions.[64]

Index Stroke Imaging Biomarkers

Traditionally, increased size and number of strokes were thought to be the drivers of cognitive impairment after stroke, though there had been no consensus on specific parameters for infarct volume or number of strokes to predict cognitive impairment.[3,65,66] As imaging improved, location of infarct and its subsequent effects on cognitive pathways have emerged as independent biomarkers for post-stroke cognitive impairment using techniques such as lesion-symptom mapping.[67–71] Voxel-based lesion-symptom mapping has shown that there is a stronger left lateralization of multiple structures involved in stroke-associated cognitive impairment.[68] Strategic locations include the dominant thalamus[70] (►**Fig. 2b** [G]), angular gyrus,[70] basal ganglia,[71] and hippocampus.[70] A strategically located stroke can have outsized detrimental effects on cognition.[71]

Laboratory Biomarkers

In the post-stroke setting, laboratory biomarkers may aid in diagnosis and prognostication of post-stroke cognitive impairment. Unfortunately, a blood test of one molecular marker may not be sufficient.[72] Inflammatory markers have been evaluated as possible biomarkers for cognitive impairment after stroke. In subcortical SVD, inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate (ESR), and interleukin levels may prove useful.[73] One recent study indicated that ESR elevation after stroke was associated with worse performance on cognitive tests.[74]

Neurofilament light chain (NFL) is a cytoskeletal protein in neurons, whose concentration is elevated in serum after acute ischemic stroke.[75] NFL is also elevated in patients with both inherited and sporadic SVD, and levels have been related to processing speed.[76] Matrix metalloproteinases (MMP) are important in the degradation of extracellular matrix and have been associated with subcortical SVD as a possible biomarker.[73] High MMP-9 in the serum has been associated with decreased Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores 3 months after stroke.[77] Elevated homocysteine has been associated with cognitive impairment; however, supplementation with B vitamins in clinical trials failed to improve cognition despite lowering homocysteine.[78]

Genetic factors can influence development of post-stroke cognitive impairment. The most strongly associated genetic factors of post-stroke cognitive impairment include those genes that cause inherited SVDs.[79] An example of this group of diseases is CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy), caused by a mutation in NOTCH3 gene that encodes a transmembrane receptor involved in remodeling of vascular smooth muscle and angiogenesis, resulting in significant SVD, migraine, strokes, and cognitive impairment.[80] Similar

conditions include CARASIL, autosomal dominant HTRA1-related cerebral SVD, COL4A1/2, FOXC1/PITX2, Fabry disease, and TREX-related disease.[79,81] In addition to single-gene disorders, other genetic factors, including the ε4 allele of the APOE genotype, may play a role in post-stroke cognitive impairment, which likely reflects a connection between AD and VaD.[82]

Mechanisms of Post-Stroke Cognitive Impairment

There is debate regarding the relative influence of underlying vascular risk factors versus the index stroke on the development of post-stroke cognitive impairment. One analysis showed that ≥3 vascular risk factors increased the risk of dementia or death by fourfold in the elderly.[83] Similarly, an analysis of the Rotterdam cohort determined that 39% of recurrent strokes and 10% of post-stroke dementia cases were attributable to pre-stroke vascular risk factors.[84]

Stroke may also increase susceptibility to further damage through neurodegeneration.[9] Hypoperfusion related to cerebral atherosclerosis may enhance the production of amyloid β peptide[85] and disrupt the blood–brain barrier, which in turn reduces perfusion and accelerates neurodegeneration in a cyclical manner.[86] Patients with AD pathology have considerably more intracranial atherosclerosis than those with normal aging or other neurodegenerative diseases.[87,88] Amyloid β has been shown to constrict isolated blood vessels. Cerebral ischemia facilitates amyloid plaque formation and tau phosphorylation and may impair the clearance of amyloid β.[6]

There are conflicting results of studies on the interaction between pre-stroke cognition and the development of post-stroke dementia.[89,90] It has been suggested that the relationship may depend on baseline performance within specific cognitive domains rather than global cognitive performance. One study found that high pre-stroke executive function was associated with a lower risk of dementia overall; however, stroke had a greater impact on the risk of post-stroke dementia in those with high pre-stroke executive function. Conversely, pre-stroke memory performance did not significantly influence the effect of stroke on risk of post-stroke dementia.[89] Baseline executive or memory deficits more than double the risk of dementia after stroke.[83] The effect of pre-stroke cognitive function, in particular executive function, on post-stroke cognition raises the concept of cognitive reserve: those with higher pre-stroke cognitive performance can lose more before showing dementia. Cognitive reserve encompasses the brain's ability to maintain cognitive function despite the presence of pathology, which is strongly influenced by age, education, and intellectual and physical activity.[91] Bilingualism, which may contribute to cognitive reserve, has been shown to lead to better cognitive outcomes after stroke.[92]

Outcomes with Post-Stroke Cognitive Impairment and Dementia

Cognitive decline after stroke typically occurs acutely with a global decline, followed by a trajectory of accelerated decline over years.[10] In the first months after stroke, there may be improvement in cognition.[93,94] Transient cognitive impairment has also been observed in the first 7 days after transient ischemic attack and minor stroke, and is associated with the later development of post-stroke dementia.[26] Similarly acute delirium, which has an incidence of ~10 to 48% during hospitalization for stroke,[95] is also associated with post-stroke dementia.[26] In a cohort of over 20,000 patients, the rate of post-stroke cognitive decline was significantly faster than pre-stroke cognitive decline.[10] In the same cohort, accelerated cognitive decline over a median follow-up of 8.2 years was greater in older individuals and those with cardioembolic stroke.[96] An analysis of a cohort including over 9,000 patients without baseline stroke or dementia demonstrated that those who experienced an index stroke had faster annual rates of *pre-stroke* cognitive decline than their stroke-free counterparts, and the slope of *post-stroke* cognitive decline was even steeper than the pre-stroke decline.[97] This suggests the presence of baseline covert processes such as silent cerebrovascular damage or poorly treated vascular risk factors contribute to cognitive decline.

Cognitive impairment is associated with poor long-term survival after stroke.[98,99] Within the Action on Secondary Prevention Interventions and Rehabilitation in Stroke (ASPIRE-S) cohort, patients with cognitive impairment (defined as MoCA <24) diagnosed 6 months post-stroke had a significantly increased adjusted mortality rate at 5 years, with the risk increasing as MoCA scores decreased.[98] In another cohort,[99] cognitive impairment (defined as MMSE ≤25) diagnosed 3 months post-stroke predicted poor long-term survival up to 12 years (4.4 vs. 9.7 years survival). Deficits in executive and visuospatial function were the neuropsychological domains most predictive of poor post-stroke survival (5.8 vs. 10.1 years survival and 5.6 vs. 10.1 years survival, respectively).[99] Although the mechanism of this relationship is not known, it is possible that executive dysfunction may serve as a surrogate for SVD, which has been shown to be associated with reduced survival.[100] Additionally, it is possible that executive dysfunction may lead to behavior that negatively affects survival, such as reduced adherence to medical and rehabilitation recommendations or strain in social support.

Detecting Pre- and Post-Stroke Cognitive Impairment

Detection of cognitive impairment in the setting of stroke can be made with several validated screening tools (►**Table 2**). Premorbid cognitive impairment can be identified reliably utilizing the Informant Questionnaire for Cognitive Decline in the Elderly (IQ-CODE). IQ-CODE has been utilized in studies for diagnosing cognitive impairment in stroke.[101]

In 2006, the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network compiled standards for the evaluation of cognitive impairment after stroke, called Vascular Cognitive Impairment Harmonization Standards.[102] Within these standards, there are three protocols. The protocols were designed to be performed by professionals in neuropsychology, focusing on executive function. The 5-minute protocol was designed to be a quick screening performed in the office or at the bedside by a variety of healthcare professionals.[102]

Table 2 Features of VCI screening tools

Screening tool	Components of the assessment
IQ-CODE (short version)	16 items on cognitive change over 10 years by informant: Memory Learning ADLs
VCIHS (30 minutes protocol)	Semantic fluency Phonemic fluency Digit symbol-coding Verbal learning test Depression scale Neuropsychiatric inventory Supplemental: MMSE, trail making test
VCIHS (5 minutes protocol)	MoCA subtests: Immediate and delayed memory Orientation Phonemic fluency
MMSE	Orientation Memory (registration, delayed recall) Attention (serial sevens) Language (naming, repetition, writing) Visuospatial: shape drawing
MoCA	Visuospatial/executive (i.e., trail making, clock drawing) Memory (registration, delayed recall) Attention (digit span, serial sevens) Language (naming, repetition, phonemic fluency) Abstraction Orientation
OCS	Language (naming, semantic fluency, reading) Orientation Memory (delayed, verbal, episodic) Number processing Attention and executive function (task switching) Praxis Visual fields

Abbreviations: ADLs, activities of daily living; IQ-CODE, Informant Questionnaire for Cognitive Decline in the Elderly; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; OCS, Oxford Cognitive Screen; VCI, vascular cognitive impairment; VCIHS, Vascular Cognitive Impairment Harmonization Standards.

Many studies have evaluated bedside testing of cognition to diagnose post-stroke cognitive impairment and predict outcomes. The MoCA and the MMSE are the two screening tests most commonly used in clinical and research settings. Because of the greater emphasis on executive function in the MoCA compared with the MMSE, some argue that the MoCA is the better screening test.[103] In a study of 463 patients with stroke or TIA, 45% had at least mild impairment on the MoCA (score $\leq$24), compared with 28% who had at least mild impairment on the MMSE (score $\leq$26). Limitations of the MoCA include limited specificity, lack of an ideal cutoff for cognitive impairment, and difficulty performing it in patients with aphasia or poor education.[104]

The Oxford Cognitive Screen (OCS) is a validated bedside tool recently developed specifically for patients after stroke. Domains of cognition are examined separately, including language, memory, number processing, attention and executive function, praxis, and visual fields.[105] The OCS has been shown to have a higher sensitivity than both the MMSE (91 vs. 35%) and the MoCA (88 vs. 78%).[106,107] The OCS requires further validation before it can be accepted as the superior tool for screening VCI.

Recovery and Treatment/Pharmacotherapy for Post-Stroke Cognitive Impairment

Stroke rehabilitation typically focuses more on physical impairment than cognitive impairment, even though cognitive impairment is reported in >50% of stroke patients at 6 months.[108] Cognitive difficulty is rated by patients as one of the most notable sources of self-reported impairments after stroke.[109] Occupational and speech therapists commonly provide cognitive rehabilitation, with aims of regaining skills and learning to compensate for areas of difficulty. The effects of cognitive interventions on domains of attention and spatial neglect may be more robust than the effects on memory, perceptual disorders, and executive dysfunction.[110,111] A meta-analysis investigating cognitive interventions post-stroke demonstrated a small to moderate effect on cognition, with domains of memory and attention benefitting the most.[112] A Cochrane review on rehabilitation of post-stroke cognitive impairment concluded that there is insufficient evidence to support clear recommendations on the topic.[111]

Treatment of vascular risk factors clearly reduces risk of recurrent stroke, but may also prevent cognitive decline; however, the data are inconsistent. One study found that intensive blood pressure and lipid lowering in patients with recent stroke did not alter cognition at 2 years, but another demonstrated that the use of lipid-lowering medication was independently associated with reduced risk of cognitive impairment regardless of age.[113,114]

Pharmacotherapies for post-stroke and VaD have been evaluated, though the US Food and Drug and Administration (FDA) has not approved a drug for this indication. Trials of donepezil, an acetylcholinesterase inhibitor, in VaD have shown significant but modest cognitive improvement; however, effects on global functioning are inconsistent.[115–117] In one donepezil trial, patients without hippocampal atrophy had improvement in cognition versus stability in those with atrophy.[115] A randomized, double-blind trial investigating the use of donepezil in CADASIL did not find a significant difference in the primary endpoint (V-ADAS-Cog score); however, there were some improvements in executive function.[118] Another acetylcholinesterase inhibitor, galantamine, has been shown to be effective in improving cognition in VaD and mixed dementia, with inconsistent effects on activities of daily living.[119,120] The benefits of other medications, such as rivastigmine (acetylcholinesterase inhibitor) and memantine (N-methyl-D-aspartate inhibitor), in VCI are not as well established.[121] The acetylcholinesterase inhibitors are modestly efficacious for AD.[122] Because most patients diagnosed clinically with AD have mixed pathology, a trial of an acetylcholinesterase inhibitor is reasonable in many cases of VCI.

Natural and herbal substances have been tried in post-stroke cognitive impairment. For instance, A Randomized Trial of Efficacy, 12 Months International Double-Blind Actovegin (ARTEMEDA) Trial, recently demonstrated a beneficial effect of Actovegin on cognition versus placebo in 248 patients with post-stroke cognitive impairment. Actovegin is a substance extracted from calf blood, and may enhance cerebral oxidative metabolism by increasing oxygen utilization and energy metabolism.[123] Other herbal drugs that have been evaluated include citicoline, Huperzine A, and vinpocetine,[121] although their effects are not well characterized.

Conclusions

VCI is a common and likely underappreciated complication of cerebrovascular disease, which often follows a progressive clinical course and is associated with decreased quality of life and increased morbidity and mortality. The presence of cognitive impairment heavily influences prognosis in patients with stroke and may influence outcome for acute reperfusion therapies. The contribution of vascular disease to the pathophysiology of dementia is becoming more recognized, although variable nosology and terminology have made systematic, collaborative research challenging. Therapies for VCI are mainly supportive at this time. Cognitive rehabilitation warrants more rigorous study. Further study of the pathophysiological relationships between cerebrovascular disease and neurodegeneration, genetic risk factors, and radiographic and blood biomarkers may yield novel treatments for this spectrum of diseases.

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Conflict of Interest
None.

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