Vascular Cognitive Impairment

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Abstract: **Cerebrovascular disease typically manifests with stroke, cognitive impairment, or both. Vascular cognitive impairment refers to all forms of cognitive disorder associated with cerebrovascular disease, regardless of the specific mechanisms involved. It encompasses the full range of cognitive deficits from mild cognitive impairment to dementia. In principle, any of the multiple causes of clinical stroke can cause vascular cognitive impairment. Recent work further highlights a role of microinfarcts, microhemorrhages, strategic white matter tracts, loss of microstructural tissue integrity, and secondary neurodegeneration. Vascular brain injury results in loss of structural and functional connectivity and, hence, compromise of functional networks within the brain. Vascular cognitive impairment is common both after stroke and in stroke-free individuals presenting to dementia clinics, and vascular pathology frequently coexists with neurodegenerative pathology, resulting in mixed forms of mild cognitive impairment or dementia. Vascular dementia is now recognized as the second most common form of dementia after Alzheimer's disease, and there is increasing awareness that targeting vascular risk may help to prevent dementia, even of the Alzheimer type. Recent advances in neuroimaging, neuropathology, epidemiology, and genetics have led to a deeper understanding of how vascular disease affects cognition. These new findings provide an opportunity for the present reappraisal of vascular cognitive impairment. We further briefly address current therapeutic concepts. (*Circ Res*. 2017;120:573-591. DOI: 10.1161/CIRCRESAHA.116.308426.)**

Key Words: cognitive impairment ■ intracranial hemorrhage ■ ischemic stroke ■ magnetic resonance imaging ■ vascular disease

As life span rises, dementia has become a growing public health issue. According to current estimates, almost 36 million people are having dementia worldwide, and this number is expected to reach 66 million by 2030 and 115 million by 2050.[1] In affluent countries, the prevalence of dementia after 65 years is 5% to 10%.[2] Vascular dementia (VaD), the second most common cause of dementia after Alzheimer's disease (AD), accounts for at least 20% of cases.[3] The prevalence of both VaD and AD rises exponentially with age, with the risk of VaD doubling every 5.3 years.[4,5] There is a decline in incidence rates of dementia in developed countries, which has in part been related to improvements in prevention and treatment

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Nonstandard Abbreviations and Acronyms	
Aβ	amyloid-Aβ
AD	Alzheimer's disease
BP	blood pressure
CAA	cerebral amyloid angiopathy
CMI	cerebral microinfarcts
cSS	cortical superficial siderosis
ePVS	enlarged perivascular space
ICH	intracerebral hemorrhages
MBs	microbleeds
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
PSD	poststroke dementia
SBI	silent brain infarcts
SVD	small-vessel disease
TCI	transient cognitive impairment
VaD	vascular dementia
VCI	vascular cognitive impairment
WMH	white matter hyperintensities
WML	white matter lesions

of vascular diseases.[2,6] Yet, the burden of dementia on patients, families, health care, and long-term care systems is growing, with costs in the United States surpassing those of cancer and heart disease.[7]

The prevalence of vascular cognitive impairment (VCI), which includes milder forms of cognitive impairment, is strongly age related. In subjects aged 65 to 84 years, the prevalence of mild forms of VCI not qualifying for dementia is higher than that of VaD.[8] Rates of conversion to dementia, institutionalization, and mortality are significantly increased in these patients, identifying patients with VCI as an important target population for prevention.[3,8–11]

Recent studies have highlighted the impact of subtle but widespread vascular injury and of ensuing changes in structural and functional connectivity on cognitive function. Also, it is now recognized that vascular injury induces secondary tissue loss in anatomically connected brain regions.[12,13] An improved understanding of the contribution of vascular diseases to cognitive decline further originates from studies combining imaging with autopsy or genetics in deeply phenotyped cohorts. Many of these data have only recently become available. We review current concepts of VCI with an emphasis on mechanisms and on aspects relevant to prevention and treatment.

Defining VCI: Diagnostic Criteria

The concept of VCI evolved from the concept of VaD, which marks the end of a continuum of clinical manifestations. There have been various efforts to define VaD, including the criteria of the *International Classification of Disease*-Tenth Revision[14] and the *Diagnostic and Statistical Manual of Mental disorders* (Fourth Edition),[15] the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et I'Enseignement en Neurosciences,[16] and the Alzheimer's Disease Diagnostic and Treatment Centers.[17]

These efforts in part reflect changes in the understanding and concept of VaD.[18] Although earlier work emphasized the role of multiple large and small infarcts (multi-infarct dementia),[19] it is now recognized that alterations in small blood vessels take center stage in VaD. These alterations are associated with more widespread injury throughout the brain[20] but most prominently involve subcortical structures. As a consequence, there have been proposals for separate diagnostic criteria for subcortical VaD.[21] A detailed discussion of individual classification systems, including *Diagnostic and Statistical Manual of Mental disorders* (Fifth Edition), is beyond the scope of this review. However, available diagnostic criteria vary with regard to sensitivity and specificity and are, thus, not interchangeable.[3,18,22–25]

VCI is a broad concept that covers the full spectrum from vascular mild cognitive impairment (vascular MCI) to VaD and includes cases with mixed pathologies, such as mixed vascular and AD-type pathologies.[3,26–28] It refers to all forms of cognitive impairment associated with cerebrovascular diseases, regardless of underlying mechanism (eg, multiple or single territorial or small infarcts, strategic infarcts) and irrespective of the occurrence of stroke symptoms. The key requirements for a diagnosis of VCI are (1) demonstration of a cognitive deficit by neuropsychological testing and (2) presence of cerebrovascular disease. The diagnosis is further classified as probable or possible depending on whether there is conclusive evidence of a causal relationship between the vascular disease and the cognitive syndrome (Table 1).

The pattern of cognitive deficits in VCI is variable, and recent criteria for VCI no longer require the presence of memory impairment, a typical feature of AD.[28–30] Hence, neuropsychological testing should cover at least 4 different cognitive domains. A diagnosis of VaD requires deficits in at least 2 domains, whereas deficits in a single domain are sufficient to diagnose vascular MCI (Table 1). The latter can be classified into 4 subtypes: amnestic, amnestic plus other domains, nonamnestic single domain, and nonamnestic multiple domains. An abnormal test result is usually defined as ≥1 SD below the mean of a cognitively healthy control population.[31] Some definitions of VCI require a subjective report of a cognitive decline by the patient or an informant.

Diagnosing vascular disease of the brain is usually straightforward, and in some cases, the relationship with the cognitive syndrome is clear; this includes (1) hereditary forms of VCI, particularly when manifesting at an early age, and (ii) cases of poststroke dementia (PSD), when the patient was cognitively normal before the stroke. In many other cases, this relationship remains uncertain, that is, in patients without any clinical history of stroke or in patients who develop progressive cognitive decline months or years after stroke. Aspects that argue for a relationship include extensive (multiple or large) vascular lesions (infarcts, hemorrhages, white matter lesions [WML]), lesions in strategic brain regions, signs of cerebral amyloid angiopathy (CAA) on neuroimaging, and specific clinical features, such as a stepwise decline of cognitive functions or prominent deficits of executive functions and processing speed.[26] However, these aspects have not been operationalized in current diagnostic criteria.[3]

Table 1. Diagnostic Criteria for Vascular Cognitive Impairment (VCI)*

VCI refers to all forms of cognitive deficits of vascular origin ranging from MCI to dementia. Diagnosis must be based on cognitive testing involving a minimum of 4 cognitive domains, including executive/attention, memory, language, and visuospatial functions.
Vascular dementia (VaD) requires a decline in cognitive function and a deficit in performance in ≥2 cognitive domains that are of sufficient severity to affect activities of daily living.
Vascular mild cognitive impairment (VaMCI) includes 4 subtypes: amnestic, amnestic plus other domains, nonamnestic single domain, and nonamnestic multiple domain; VaMCI should be based on the assumption of a decline in cognitive function. Activities of daily living may be normal or mildly impaired.
Probable: A diagnosis of probable VaD or VaMCI requires the following:
(1) Imaging evidence of cerebrovascular disease and (a) a clear temporal relationship between a vascular event (eg, stroke) and onset of cognitive deficits or (b) a clear relationship between the severity and pattern of cognitive impairment and the presence of diffuse subcortical vascular pathology;
(2) Absence of a history of gradually progressive cognitive deficits, suggesting the presence of neurodegenerative disease.
Possible: A diagnosis of possible VaD or VaMCI requires imaging evidence of cerebrovascular disease and should be made if there is no clear relationship between vascular disease and cognitive impairment, if the criteria for probable VaD or VaMCI are not fulfilled, if aphasia precludes proper cognitive assessment, or if there is a history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.
Unstable VaMCI: subjects with probable of possible VaMCI whose symptoms revert to normal

MCI indicates mild cognitive impairment.

*The key distinction between VaD and VaMCI is the degree of the functional deficit. The criteria cannot be used in subjects with delirium or an active diagnosis of substance abuse. Criteria were derived from Gorelick et al.[3]

Reversibility

Occasionally, patients with VCI may return to normal cognition particularly when cognitive deficits occurred in the context of an acute stroke,[32] depression,[33–35] heart failure,[36] or autoimmune disorders.[37] VCI is reversible in ≤20% of patients after stroke, with the highest rate of recovery seen shortly after stroke.[32] Transient cognitive impairment (TCI) not necessarily returning to normal cognitive function is even more frequent and associated with a 5-fold increased risk of developing severe dementia in the next 5 years.[38,39] However, TCI should not be equated with delirium, one of the causes underlying TCI found in ≤25% of hospitalized stroke patients.[40,41] Both delirium and TCI are associated with worse outcomes.[38,42] Reversal of cognitive impairment is further seen in patients successfully treated for depression.[33,43]

Mechanisms

In principle, any of the multiple etiologies of stroke (small-vessel disease [SVD], large-artery atherosclerosis, cardioembolism, or other less common etiologies of stroke) can cause VCI.[44] However, neuroimaging and pathological studies have identified typical settings of vascular causes and brain parenchymal lesions that are associated with cognitive impairment (Figure 1). This has provided a framework of mechanistically defined VCI categories.

Multiple Infarcts (Multi-Infarct Dementia)

The presence of multiple small or large infarcts has for long been recognized as a cause of dementia.[19] Larger infarct volumes and a higher number of territorial or small subcortical infarcts are associated with worse cognitive performances and higher risks of dementia.[19,45–47] There is no clear threshold for an overall volume of brain lesion required for the occurrence of VCI or VaD. This relates to several factors: first, some brain regions are more eloquent with regard to cognitive functions than others. Second, many patients have comorbid conditions, such as AD.[48] Third, there are interindividual variations in the ability to compensate for both vascular and neurodegenerative pathologies.[49–51] Nevertheless, multi-infarct dementia remains a valid concept.

Strategic Infarcts (Strategic Infarct Dementia)

A single small infarct may cause severe cognitive deficits when located in a strategic brain region. Classical anatomic locations for strategic infarcts include the thalamus, angular gyrus, and basal ganglia, including the caudate nucleus and globus pallidus.[52–57] Voxel-based magnetic resonance imaging (MRI) studies have highlighted a key role of specific white matter tracts, in particular the anterior thalamic radiation and forceps minor in VCI.[58–60] This finding matches earlier reports on patients who developed dementia in the context of small infarcts in the internal capsule[54,61] and anterior part of the corpus callosum.[53,62] The available data are still insufficient to draw a complete picture of strategic brain regions and networks relevant to VCI. However, it is now recognized that most strategic locations integrate into larger networks or cortico-subcortical loops with a presumed role in cognition. It has further become clear that the same structures are also vulnerable to WML[58–60] and intracranial hemorrhages.[53]

WML and Lacunes (Subcortical Ischemic VaD)

By far, the most common cause of VCI is cerebral SVD, which typically manifests with WML and lacunes. MRI shows hyperintense signals on T2-weighted and fluid-attenuated inversion recovery images termed white matter hyperintensities (WMH) and small cystic cavities with a signal behavior identical to cerebrospinal fluid (lacunes; Figure 2). In the general population, prevalence rates for WMH rise from 50% to 95% around 45 and 80 years of age, respectively.[63,64] Small brain infarcts are also common[65] and like WMH have been shown to be associated with cognitive deficits and dementia.[65–67] A correlation between the burden of subcortical ischemic lesions and lower cognitive performances has been documented both in population-based cohorts[68,69] and in hospital-based samples,[67,70] including patients with pure SVD,[71] with some studies suggesting a threshold effect.[68,72,73] However, such

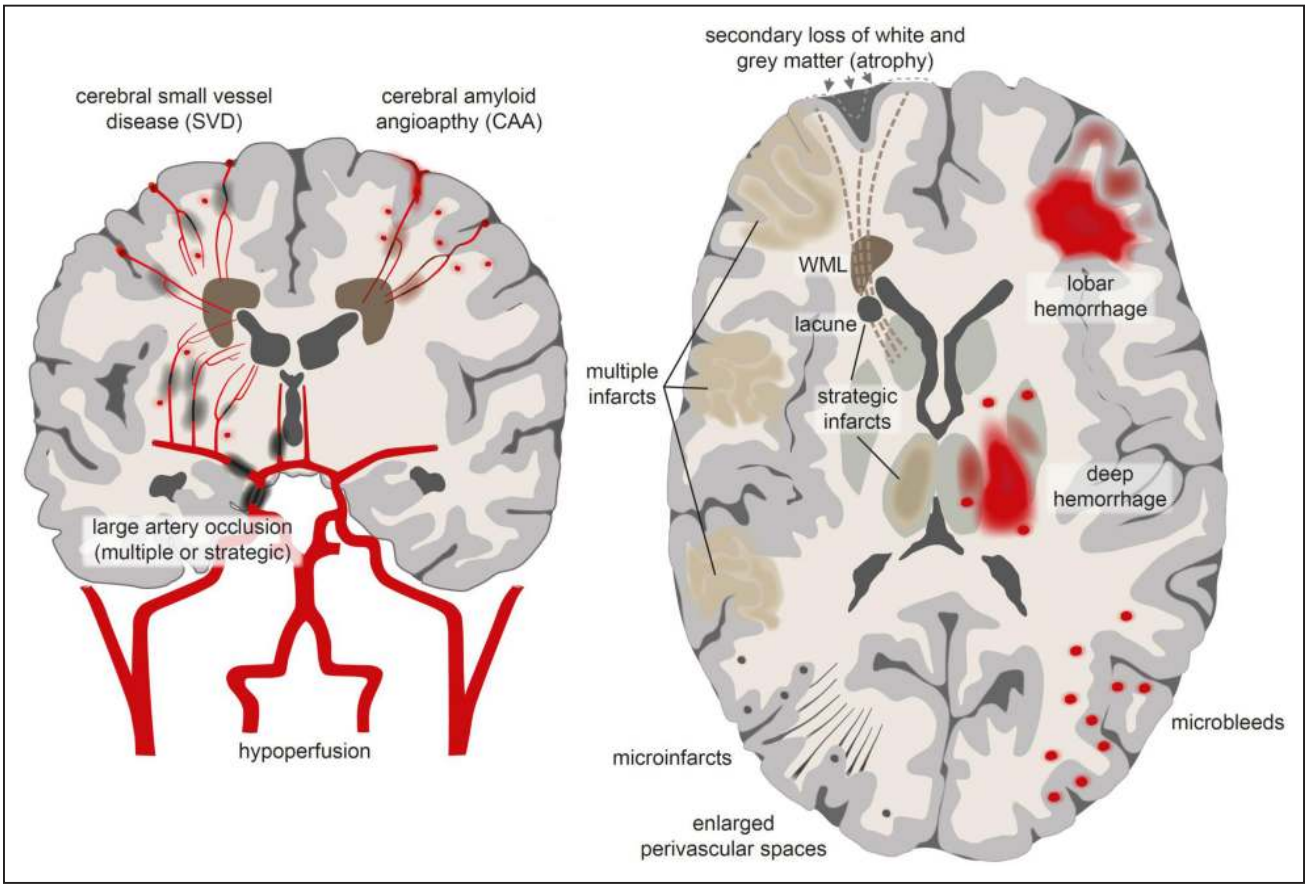

Figure 1. Major mechanisms underlying vascular cognitive impairment (VCI). A, Vascular causes. **B**, Brain parenchymal lesions associated with VCI. For explanations, see text. WML indicates white matter lesion (graphical realization: Antonia Weingart, Institute for Stroke and Dementia Research).

thresholds are difficult to define given the heterogeneity of lesions and impact of location.

Because of the prominent appearance of WMH and lacunes on MRI, their anatomic location within white and deep gray matter, and a characteristic profile of associated clinical features, investigators have coined the terms subcortical ischemic vascular disease and subcortical ischemic VaD.[20,21,74–76] However, the consequences of SVD may extend into the cortex, manifesting both as microscopic vascular lesions and cortical atrophy.[77–79] Cortical changes are now considered a clinically relevant component of SVD.[13,77,80] Still, WML and lacunes represent the most prominent manifestations of SVD. Pathologically, WML represent variable degrees of axonal loss, demyelination, and gliosis. However, imaging findings should not be equated with specific pathological changes.[81] Also, MRI captures aspects that are usually not in the focus of pathological assessment, such as edema.[82]

Brain Hemorrhages (Hemorrhagic Dementia)

Both macroscopic intracerebral hemorrhages (ICH)[83,84] and microbleeds (MBs)[85] have been associated with cognitive decline or dementia, which may manifest before or after ICH.[84,86] The underlying vascular cause in deep ICH typically is hypertensive SVD,[84] whereas lobar ICH is associated with CAA.[84] These conditions will be discussed later.

Global Hypoperfusion (Hypoperfusion Dementia)

Global reductions in cerebral perfusion can result in transient or permanent ischemia and, hence, cognitive deficits.

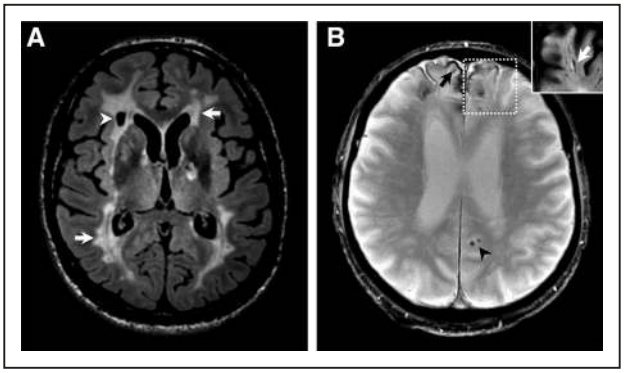

Figure 2. Magnetic resonance (MR) imaging changes associated with vascular cognitive impairment (VCI). A, Fluid-attenuated inversion recovery (FLAIR) image of a 64-year-old male patient with vascular dementia (VaD) showing extensive white matter hyperintensities (white arrows) and a lacune in the right frontal white matter (white arrowhead). **B**, T2*-weighted gradient echo scan of a 52-year-old female patient with VCI, demonstrating 2 microbleeds in the left occipital cortex (black arrowhead) as well as superficial siderosis in the frontal cortex predominantly on the right side (black arrowhead); inset: FLAIR image of the left frontal cortex displaying an enlarged perivascular space. In both cases, there is some indication of brain atrophy as reflected by a widening of sulci.

Carotid-artery occlusion or high-grade stenosis may cause cognitive impairment even in the absence of macroscopic brain lesions.[87–89] In the RECON trial (Randomized Evaluation of Carotid Occlusion and Neurocognition), hemodynamic failure (as defined by an increased oxygen extraction fraction measured by positron emission tomography imaging) on the side of carotid-artery occlusion was independently associated with cognitive impairment.[90] Studies on patients with unilateral asymptomatic severe carotid-artery stenosis have demonstrated decrements in structural brain connectivity ipsilateral to the stenosis[88] and an increased risk of cognitive decline.[89] Other causes of cognitive impairment induced by global reductions in cerebral perfusion include cardiac arrest, severe cardiac failure, arrhythmias, and severe hypotension.[91–94] Pathologically, global hypoperfusion has been associated with border zone infarcts, cortical laminar necrosis, and hippocampal sclerosis.[95]

Mixed Vascular and AD (Mixed Dementia)

Many patients with MCI or dementia have mixed pathologies.[48,49,96,97] This relates to the high prevalence of both vascular and AD pathology in the elderly and to shared risk factors.[11,98,99] In the Religious Orders Study and the Rush Memory and Aging Project, mixed vascular and AD-type pathology was the predominant finding in patients diagnosed with dementia.[48] Individuals with multiple pathologies were 3× more likely to be demented than were those with 1 pathology. In most cases, it is difficult to estimate their relative contribution to cognitive decline. However, vascular brain lesions lower the threshold of AD pathology required to induce dementia.[56,100–102] Conversely, AD pathology increases the risk of dementia after stroke[103] and contributes to cognitive decline in patients with VCI.[104] Earlier studies have suggested a multiplicative effect between vascular and AD-type pathology on cognitive decline,[56] whereas recent studies indicate that the effects are additive.[49,100,105] Yet, the relationship may be more complex. Novel autopsy data show that both large- and small-artery disease are associated with AD dementia independent from infarcts.[106]

Specific Arteriopathies

Several well-defined arteriopathies, such as hereditary and sporadic forms of CAA[107–109] or hereditary forms of ischemic SVD,[110] typically manifest with cognitive decline or dementia. The most frequent monogenic cause of VCI is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, a severe SVD caused by NOTCH3 mutations.[111–113] Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy represents a pure form of VCI. As such, this condition has greatly contributed to the understanding of VCI mechanisms. Another, less common arteriopathy associated with cognitive decline and dementia is cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, a condition caused by HTRA1 mutations.[114,115]

Silent Brain Lesions of Vascular Origin: Impact on Cognition

Silent Brain Infarcts

Silent brain infarcts (SBI), that is, infarcts without attributable acute neurological symptoms, are common in elderly people. Their prevalence increases from ≈10% to 40% in subjects aged 65 and 90 years, respectively, and the prevalence is even higher in patients with vascular risk factors.[65] Most SBI are lacunes attributable to SVD. In the Rotterdam scan study, the presence of SBI at baseline doubled the risk of dementia,[66] and similar figures were obtained in the Framingham Offspring study.[116] In Rotterdam, the presence of SBI was further associated with worse performance on cognitive testing and a steeper decline in cognitive function. Thalamic infarcts were associated with a decline in memory performance, whereas non-thalamic infarcts were associated with a decline in psychomotor speed.[66] A strategic role of silent thalamic infarcts is further suggested by an autopsy study in 72 subjects that found silent thalamic and basal ganglia lacunes to be associated with clinical dementia rating scores obtained before death. The impact of SBI on cognition might be lower in younger subjects because there was no association in the PURE study (Prospective Urban Rural Epidemiological), which included subjects aged 40 to 75 years.[117]

Microinfarcts: Invisible Lesions

Only recently, investigators have recognized the impact of cerebral microinfarcts (CMI) on cognitive function and risk of dementia. CMI are small ischemic lesions not visible to the naked eye (typically <1 mm) but detected microscopically during pathological examination, where they may be cystic or incomplete[47,79] (Figure 3). These lesions represent the most widespread form of brain infarction and are generally attributed to SVD, although other mechanisms, such as microemboli, cerebral hypoperfusion, or vasoconstriction, are also discussed as potential causes. The presence of 1 or 2 CMI in routine neuropathological specimens implies the presence of hundreds of CMI throughout the brain.[118] CMI may be located in cortical or subcortical regions and are particularly common in patients with VCI. However, they are also frequent in AD patients and in unselected elderly people.[119,120] CMI have been shown to be associated with an increased risk of dementia both in hospital-based studies and in prospective cohorts. In a hospital-based series of 43 autopsy cases with low or intermediate levels of neurofibrillary tangle pathology, CMI explained most of the variance in clinical dementia rating scores even when controlling for other vascular lesions.[121] In accord with this, a recent meta-analysis of data from the Honolulu-Asia Aging Study,[122] Religious Orders Study,[123] and other community-based studies found the prevalence of CMI to be nearly twice as high in people who died with dementia.[79] The profile of cognitive deficits associated with CMI has not been studied in detail, but in one study, they were found to be associated with disturbances in episodic memory, semantic memory, and perceptual speed.[123] Quantifying CMI in vivo remains a challenge: they are best detected on ultrahigh-field MRI at 7 T,[124] but may occasionally be seen on conventional 3T scans.[125,126] MRI is much more sensitive in detecting acute small infarcts detected on diffusion-weighted imaging, and indeed, a recent study suggests that such small diffusion-weighted imaging lesions are indicative of an annual incidence of hundreds of new CMs.[127]

Microbleeds and Superficial Siderosis

MBs are small, round, well-defined foci of MRI signal void appearing black on gradient echo T2*-weighted scans. MBs are detected in 10% to 15% of elderly subjects[128–130] and in ≤80% of patients with VaD.[131] They are generally considered

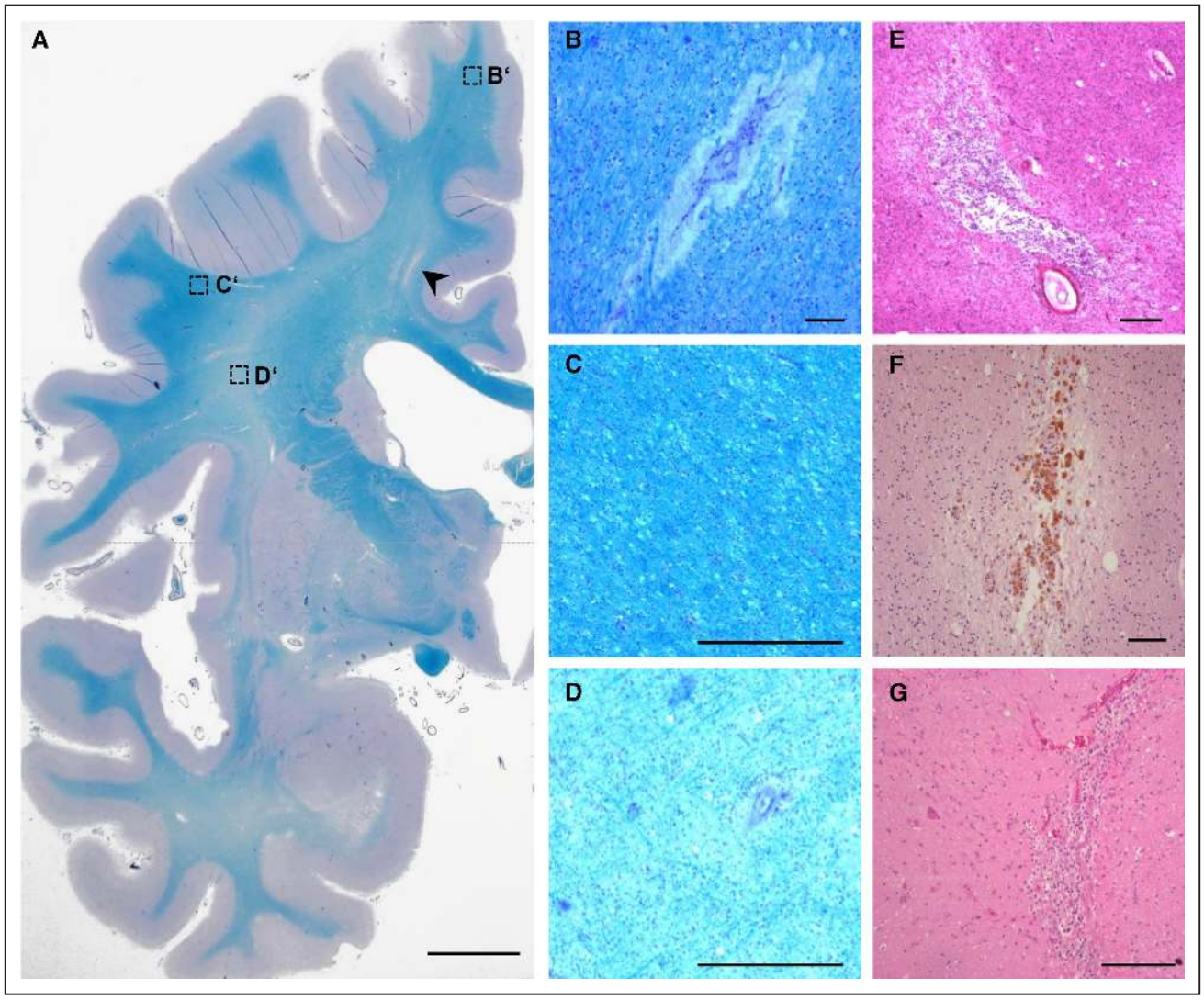

Figure 3. Pathological findings associated with vascular cognitive impairment (VCI). A, Hemisphere section of a patient with small-vessel disease and extensive white matter rarefication (Luxol fast blue periodic acid Schiff-reaction [LFB-PAS] stain, scale bar 1 cm); the arrowhead marks a lacunar infarct; boxes correspond to higher magnifications in **B**, **C**, and **D**. **B**, Enlarged perivascular space (LFB-PAS stain, scale bar 200 μm). **C**, Mild white matter rarefication (pallor; LFB-PAS stain, scale bar 500 μm). **D**, Marked white matter rarefication (pallor; LFB-PAS stain, scale bar 500 μm). **E**, Lacunar infarct (hematoxilin and eosin stain, scale bar 500 μm). **F**, Microhemorrhage with hemosiderin-loaded macrophages (hematoxilin and eosin stain, scale bar 200 μm). **G**, Microinfarct (hematoxilin and eosin stain, scale bar 200 μm). Images were kindly provided by Thomas Arzberger and Karl Bise, Institute for Neuropathology and Prion Research, LMU, Munich.

a manifestation of SVD.[132,133] They have been related to focal deposits of iron-positive blood breakdown products, although recent data suggest that the underlying pathology and mechanisms may be more heterogeneous.[134] A growing body of evidence suggests that MBs may affect cognition. A higher number of MBs is associated with lower cognitive scores even when adjusting for vascular risk factors and other markers of SVD.[130] They are also associated with an increased risk of VaD.[128] In patients with vascular risk factors, multiple MBs were associated with incident dementia.[135] An association between presence or number of MBs and cognitive function was further found in patient with transient ischemic attack or stroke,[136] in non-demented elderly patients with SVD,[137] and in patients with symptomatic SVD.[138] The mechanisms by which MBs affect cognition are still debated as is the impact of MB location on cognitive impairment or dementia.[128–130,135] However, there is some evidence that MBs disrupt structural connectivity and, hence, network function.[139–141]

Cortical superficial siderosis (cSS) represents linear deposits of blood-breakdown products within the subarachnoid space, the leptomeninges, and the superficial cortical layers.[142] cSS is intimately connected to CAA.[143] The correlate on gradient echo T2*-weighted scans is a characteristic dark (signal void) rim along the cortical surface (Figure 2). The prevalence of cSS in non-demented elderly subjects is around 0.5%,[142,144] whereas the frequency in patients recruited through memory clinics is much higher ranging from 2% to 6%.[145–147] In a study from South Korea,[147] cSS was similarly frequent in patients clinically diagnosed as subcortical VCI and AD-related cognitive impairment, but cSS was exclusively present in patients

who had a positive amyloid–positron emission tomography imaging scan. CSS was associated with other markers of CAA, including a strictly lobar location of MBs and the presence of an apolipoprotein E ε2 allele. cSS has further been reported to be associated with the apolipoprotein ε4 allele, which is also consistent with the known association between cSS and CAA. Whether cSS contributes to cognitive decline has to date not been studied in detail.

Subtle Loss of Microstructural Integrity

Among the earliest manifestations of SVD is a subtle loss of microstructural tissue integrity. These early stages are not detected by conventional MRI but are captured by diffusion tensor imaging.[81] Measures of this technique can be quantified across the entire brain or within selected brain regions and are among the markers that correlate best with cognitive function and cognitive decline in regression models, accounting for age, WMH, lacunes, and other disease markers.[148–150] Moreover, the same measures enable identifying individuals at risk for developing cognitive decline even when measured within tissue appearing normal on conventional MRI.[151] This may allow for a completely new treatment perspective because current approaches usually fail when treatment is started in patients with advanced pathology. A valuable addition in this context has been the introduction of novel tools to quantify microstructural tissue damage across major white matter tracts in an automized way.[152]

Enlarged Perivascular Spaces: Disentangling the Influence of Different Pathologies on Cognitive Function

Enlarged perivascular spaces (ePVS) are a frequent MRI finding in elderly people, especially in subjects with vascular risk factors and in patients attending memory clinics[81,153,154] (Figures 1 and 2). ePVS are associated with cognitive function and dementia.[155–157] Typical locations include the centrum semiovale, basal ganglia, hippocampus, and mesencephalon.[153] ePVS are associated with markers of SVD, including WMH, lacunes, and retinal microvascular calibers.[154,157–160] However, they are not specific for SVD but also associated with other conditions, including AD and multiple sclerosis.[153] Proposed mechanisms for enlargement include brain atrophy, hypertension, inflammation, and changes in perivascular flow.[153,161]

Disentangling the influence of different lesions and imaging markers such as ePVS on cognitive function remains difficult because most markers are associated with other markers through shared disease processes (eg, SVD). Also, some markers, such as ePVS, may originate from multiple disease processes that may run in parallel. There are additional factors that influence the consequences of lesions on cognitive function, such as lesion location, the presence of subtle, unrecognized pathology, and cognitive reserve (Figure 4). Finally, some pathologies such as atrophy may in part originate from other pathologies (see next paragraph).

Secondary Neurodegeneration: The Role of Brain Atrophy

Aside from causing local tissue damage, ischemic infarcts can induce neurodegenerative changes in remote brain regions.[12,13,162]

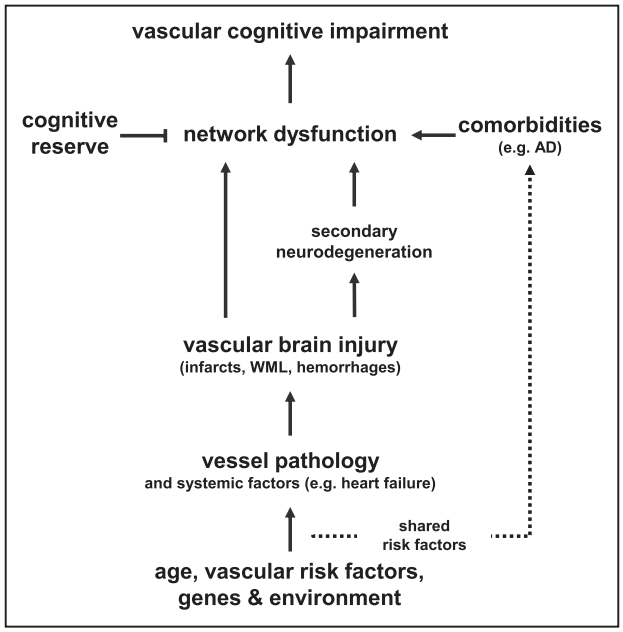

Figure 4. Key determinants of vascular cognitive impairment. For explanations, see text. AD indicates Alzheimer's disease; and WML, white matter lesion.

Secondary neurodegeneration after subcortical ischemic infarcts is mediated by a degeneration of neuronal fiber tracts connecting the initial vascular injury with distant gray matter and resulting in focal or widespread loss of white matter and cortical thinning[13] (Figure 1). The mechanisms underlying secondary gray matter loss are poorly understood but possibly involve transsynaptic effects[57,163] and inflammatory reactions.[164] Another potential mechanism is retrograde degeneration of cortical neurons projecting to subcortical structures as suggested by the selective loss of pyramidal cell volumes in layers III and V of the dorsolateral prefrontal cortex in patients with PSD.[165] Changes of cortical morphology on MRI include a reduction of cortical thickness,[13,166] as well as alterations in sulcal morphology.[77,80] Interestingly, the spatial patterns of cortical thinning and cognitive trajectories associated with amyloid-β (Aβ) deposition differ from those associated with lacunes.[167]

Brain atrophy is among the strongest predictors of cognitive impairment in patients with pure vascular disease,[80,168] and a growing body of evidence suggests that the effects of subcortical ischemic lesions on cognitive functioning are mediated by the ensuing loss of cortical gray matter.[169–171] In the Austrian Stroke Prevention Study, associations between changes in WMH load and cognitive functioning were no longer significant when adding change in brain volume to the models.[172] Together, these observations identify secondary neurodegeneration as a target for future therapeutic interventions.[173]

Structural and Functional Connectivity: Network Dysfunction Takes Center Stage

Cognitive functions emerge from communication between cortical and subcortical brain regions.[174,175] Vascular lesions may disrupt network structure and function by injuring white matter, cortical gray matter (hubs), or subcortical gray matter. Indeed, recent work suggests that the effects of vascular

lesions on cognitive function are mediated through alterations in structural and functional connectivity (Figure 4).

Structural connectivity is assessed by diffusion imaging, whereas there are several ways to measure functional connectivity, including resting state functional MRI and electroencephalography. Several MRI studies have looked at the relationship between vascular lesions, structural connectivity, and cognitive function, with most work done in patients with cerebral SVD. These studies consistently found an association between the burden of SVD-related brain lesions and reduced network efficiency.[140,170,176] Even more important, network efficiency was found to mediate the effects of SVD-related MRI lesions on cognitive function, and similar results were reported for patients with CAA.[141] Some studies have looked at regional connectivity, regional cortical thickness, and executive function. In accord with earlier observations,[169,171] a recent study found reductions in frontal network efficiency to mediate the effects of SVD-related lesions on frontal gray matter loss, as well as on executive dysfunction.[170] The clinical relevance of these observations is highlighted by the observation that lower network efficiency predicts conversion to dementia along with higher age and lower hippocampal volume.[177]

Functional connectivity has been less well explored. However, there is some evidence that the effects of vascular lesions on MCI are in part mediated by altering functional connectivity,[178–180] and this has specifically been shown for frontal brain regions.[181] These findings add to the growing notion that disturbances in large-scale networks take center stage in determining cognitive decline.[182,183]

Poststroke Dementia

Stroke doubles the risk of dementia, with risk being highest immediately after stroke and remaining high thereafter.[103,184–186] In a large population-based study, incident stroke was associated with an acute decline in cognitive function and both an accelerated and persistent decline of cognitive function within the following years.[187]

PSD refers to all types of dementia after stroke, irrespective of its cause and onset, that is, prior to, parallel with, or after stroke.[103,185,186] Prevalence estimates for prestroke dementia range from 9.1% in population-based studies to 14.4% in hospital-based studies.[103] Estimates for the prevalence of PSD largely vary depending on the setting (eg, population-based versus hospital-based), interval from stroke, and whether patients with recurrent stroke, prestroke dementia, and aphasia are included.[103] In previous hospital-based studies, the pooled prevalence of PSD ≤1 year after stroke was 20%, when excluding patients with prestroke dementia. However, these patients were mostly recruited in the 90s, and more recent studies have reported lower prevalence rates possibly because of therapeutic improvements and changes in case mix.[188,189] The long-term incidence of dementia starting from 3 months after stroke has been estimated to be 3% to 6% per year,[103,190] with slightly lower rates reported for patients with transient ischemic attack and minor stroke.[191]

Milder deficits of cognitive function in at least 1 cognitive domain (poststroke MCI) are much more common after stroke.[188,192,193] A study from Helsinki found 83% of stroke survivors to show impairment in at least 1 cognitive domain, with 50% of patients showing deficits in multiple (≥3) domains when tested 3 months after stroke.[192] Cognitive deficits in the first days after an acute stroke may be transient[32,194] and, in some cases, reflect delirium.[40,41] TCI delirium, and poststroke cognitive impairment all are associated with poor outcome, including institutionalization and mortality.[38,42,195,196]

Risk factors for PSD include increasing age, female sex, prestroke cognitive decline, poststroke cognitive impairment, recurrent stroke, multiple vascular risk factors (in particular, atrial fibrillation, smoking, and diabetes mellitus), depression, early seizures, and low educational status.[103,185,189–191,197,198] The presence of at least 4 vascular risk factors increases the risk of dementia or death by 4-fold in elderly stroke survivors,[190] but the influence of vascular risk factors is probably lower than that of stroke recurrences.[199] Imaging predictors of PSD include WMH, SBI, and medial temporal lobe atrophy.[103,189,198] Interestingly, some of these factors show an even stronger association with prestroke dementia. This particularly applies to temporal lobe atrophy, which is also associated with AD. Still, several observations suggest that the cognitive deficits in PSD and poststroke MCI primarily relate to vascular pathology rather than comorbid age-related pathologies. In an autopsy study on stroke patients prospectively followed until death, ≥75% of demented subjects met current pathological criteria for VaD.[190] Also, in the to date largest study on amyloid positron emission tomography imaging and PSD, the frequency of amyloid positivity in patients who developed incident PSD was 30%, which is similar to the point estimate for healthy subjects from the same age group.[198,200] Of note, however, individuals with amyloid positivity exhibited a more rapid decline of cognitive scores in multiple domains compared with amyloid-negative patients when followed over 3 years.[201]

There are few data on the cognitive profile of PSD and poststroke MCI. Among the early and most pronounced abnormalities are deficits in attention and executive function as would be expected in patients with predominant vascular pathology. However, deficits in other domains such as orientation, memory, and language are also common, particularly in those with more severe cognitive impairment.[30] In light of a decline in mortality rates, long-term consequences of stroke are receiving more and more attention. As a consequence, recent secondary stroke prevention trials included cognitive end points to their study protocols.[202,203]

Intracerebral Hemorrhage

Because of a lower incidence and higher case-fatality rates of ICH compared with ischemic stroke, there are less data on the relationship between ICH and cognitive decline. A substantial proportion of patients admitted for ICH have preexisting cognitive impairment or dementia. Of 417 patients with ICH who were systematically assessed for preadmission cognitive status by the Information Questionnaire on Cognitive Decline in the Elderly, 14% had cognitive impairment no dementia, and 16% had dementia.[86] Among those with lobar ICH, the prevalence of preexisting dementia was 23%. Factors associated with preexisting dementia in lobar ICH were higher age, lower educational level, and cortical atrophy. Factors associated with preexisting

dementia in deep ICH were old territorial vascular lesions and a higher burden of white matter changes. The majority of patients with preexisting dementia who came to autopsy had lobar ICH. All of them had AD-type and CAA pathology, whereas the single patient with deep ICH had SVD without AD-type pathology.[86] Hence, preexisting dementia is frequent in patients with ICH and may be the consequence of 2 distinct mechanisms: neurodegeneration with AD-type pathology and CAA in lobar ICH versus vascular processes in deep ICH.

The risk of cognitive decline after ICH remains high even years after the ICH.[83,84,204,205] In a cross-sectional study on 78 ICH survivors studied at a mean of 40 months after the event, 23% had developed new-onset dementia. Cognitive impairment without dementia was observed in 77% of patients undergoing detailed testing.[204] Cognitive deficits predominantly involved episodic memory, psychomotor speed, and executive function.[204]

Longitudinal data with long-term follow-up are available from the Lille ICH cohort.[83,84] Among 167 consecutive ICH survivors without preexisting dementia, 37% were found to decline over a median interval of 4 years.[83] Factors associated with cognitive decline were previous stroke or TIA, preexisting cognitive impairment, and cortical atrophy.[83] This suggests that the causes and mechanism underlying cognitive decline after ICH are mostly already present at the time of ICH.[83] In a more recent study on 218 ICH survivors free of dementia 6 months after the acute event and followed for a median interval of 6 years, 29% developed dementia.[84] The incidence rate of dementia was much higher in those with lobar ICH compared with those with deep ICH. Predictors of new-onset dementia were disseminated cSS, cortical atrophy, a higher number of MBs, and higher age, suggesting an important role of CAA. Collectively, these findings suggest that in many ICH patients, dementia is the consequence of a chronic disease process and that avoiding the ICH may not be enough to prevent dementia.[84]

Cerebral Amyloid Angiopathies

CAA refers to a heterogeneous group of biochemically and genetically distinct conditions that are characterized by amyloid deposition in the walls of leptomeningeal and cortical arteries, arterioles, and less frequently capillaries and veins. By far, the most common form is sporadic CAA with vascular deposition of Aβ.

Sporadic Aβ-Related CAA

Aβ-related sporadic CAA is found in normal elderly subjects, in patients with AD, and in Down's syndrome.[206] Estimates for moderate to severe CAA range from ≈2% in those aged 65 to 74 years to >20% in those aged >85 years.[207–209] In patients with concomitant AD, the prevalence of CAA at autopsy is >80%.[209,210] In the population-based Honolulu-Asia Aging Study, 44.1% of patients had autopsy-proven CAA in at least 1 neocortical area. CAA was associated with more neurofibrillary tangles, more neuritic plaques, and greater probability to have at least 1 apolipoprotein E ε4 allele,[211] reflecting the known overlap with AD.

Aβ-CAA typically manifests with lobar ICH, cognitive impairment, or both.[108,212] Advanced CAA has been shown to be associated with worse cognitive performance independent of AD pathology in several autopsy studies.[211] In the largest study to date, CAA was associated with an increased rate of decline in global cognition, perceptual speed, episodic memory, and semantic memory.[213] The mechanism by which CAA causes cognitive decline are insufficiently understood but likely include ischemic injury to the white matter,[214] micro- and macrobleeds, and microinfarcts and an ensuing loss of functional and structural network integrity.[141]

Aβ-CAA is usually diagnosed on the basis of clinical and radiological findings. Radiological findings supporting the diagnosis of CAA include multiple lobar hemorrhages,[215] multiple MBs, particularly in the temporal and occipital lobes,[216] and cSS.[142,143] The diagnostic utility of amyloid positron emission tomography imaging[217,218] and measurements of Aβ levels in cerebrospinal fluid[219] seems to be rather limited. This in part relates to limited specificity in distinguishing between CAA and AD.

Hereditary Forms

There are several hereditary forms of CAA, which are characterized by specific mutations and an accumulation of specific proteins in cerebral blood vessels (reviewed in Biffi and Greenberg[209]). Clinical presentations differ between conditions but most of them cause dementia. Among the most thoroughly studied conditions is hereditary cerebral hemorrhage with amyloidosis, Dutch type, which is caused by a point mutation in the amyloid precursor protein gene.[220] Dementia is common and has been shown to develop independent of plaques and neurofibrillary tangles.[107] Hence, this condition provides further proof that CAA alone is sufficient to cause dementia.

Diagnostic Evaluation

Overview on Cognitive Domains to be Assessed in VCI

Typical reasons for patient referral include complaint by the patient, a related party, or health professionals. Although extensive neuropsychological assessment by a trained investigator may be optimal, a shorter bedside evaluation with a screening instrument is often more appropriate. Screening tests should cover the following cognitive domains[24]: (1) attention and processing speed; (2) frontal–executive function; (3) learning and memory; (4) language; (5) visuo–constructional–perceptual ability; (6) praxis–gnosis–body schema; and (7) social cognition.

Executive function includes various processes necessary for an effective and appropriate behavior, such as initiation, planning, hypothesis generation, cognitive flexibility, decision making, regulation, judgment, feedback utilization, and self-perception.[221] Various aspects of executive functions are assessed in the Montreal Cognitive Assessment battery using tasks adapted from the Trail Making B task, a phonemic fluency task, and a 2-item verbal abstraction task. Verbal memory includes both immediate recall (a measure of attention) and delayed recall. Although delayed recall of logical content is most closely linked to amnestic MCI and AD, delayed recall of word lists and visual content is most closely linked

to vascular brain injury.[222] Care should be taken to standardization and the availability of normative data when choosing specific test batteries.

Screening Instruments

The Mini-Mental State Examination[223] is the most widely used screening test. However, it was designed for AD and has a strong emphasis on language and memory and not on executive dysfunction, a hallmark of VCI. The Montreal Cognitive Assessment includes an evaluation of executive functions and has, thus, been recommended for use in VCI either in full length[224] or (less optimal) in an abbreviated version. It is sensitive to the cognitive profile of stroke patients, easy to administer, and available in multiple languages.[224,225] The Telephone Interview for Cognitive Status has been validated both in the general population and in patients with stroke with good sensitivity and specificity and with better performance in detecting multiple-domain versus single-domain MCI.[226,227] However, telephone interviews are limited by inability to test visuo–executive items.

Neuropsychological Assessment

The National Institute of Neurological disorders and Stroke—Canadian Stroke Network Vascular Cognitive Impairment Harmonized battery was developed by a consensus process among experts and is undergoing validation in several languages.[28] This battery aims at maximizing information obtained from relatively few tests with well-validated tasks. It is organized such that multiple measures can be derived from a single and simple test, where one brief test provides insight into different domains. The battery consists of 3 sets of tests that can be applied in 60, 30, or 5 minutes.[28] However, there are alternative test batteries. Key issues include the need to administer a broad range of cognitive tests that capture different aspects of cognitive function and that are normed for language/ethnicity, age, education, and setting.

Given the high frequency of preexisting dementia or cognitive deficits in patients with stroke, there is broad interest in determining premorbid cognitive status. The most widely used scales for this purpose are the Informant Questionnaire for Cognitive Decline in the Elderly[228] and the AD8 Screening Interview,[229] which should be completed by a related party. Cognitive symptoms must be separated from depression.[34] And again, the choice of assessment tools should depend on the setting and severity of cognitive impairment. Widely used tests for depression include the Hamilton Depression Rating Scale[230] and the Center for Epidemiological Studies Depression Scale.[231] The Geriatric Depression Scale[232] is also widely used but contains questions about cognition, which must be considered when interpreting the results. The Cornell Scale for Depression in Dementia[233] shows poor sensitivity to changes over time. The Dementia Mood Assessment Scale has high sensitivity, but relies on the rating of the interviewer.[234]

Risk Factors

A detailed discussion of risk factors for VCI, which are partly covered in previous sections and below, is beyond the scope of this review. Risk factors broadly overlap with those for stroke. The interested reader is referred to recent topical reviews[3,11] and to references provided in Table 2.

Prevention

Preventive interventions may have a modest effect at the individual level, but lead to a major reduction in the burden of VCI at the population level. Interventions include lifestyle modifications, the control of vascular risk factors, treatment of concomitant vascular disease, and established strategies for stroke prevention.[3]

Lifestyle Factors

A lower education level is associated with an increased risk of dementia of any cause (vascular, degenerative, or mixed). However, there is no evidence for a protective influence of education, cognitive training, and any other structured cognitive intervention on the occurrence of vascular or degenerative brain lesions. Available data suggest that education attenuates the impact of brain pathology on clinical expression rather than influencing the occurrence or progression of brain pathology.[11,50] Whether smoking cessation reduces the risk of cognitive decline remains uncertain. However, former smokers show a reduced risk of cognitive decline when compared with current smokers.[11,237]

The most convincing evidence for an influence of diet on VCI risk comes from studies on vitamin E, acting as an antioxidant, fish, n-3 fatty acids, polyunsaturated fats, B12 vitamin, and folates, that is, components found in Mediterranean diet.[249] Several prospective observational studies have shown that adherence to such a diet is associated with a lower risk of AD and cognitive decline. However, there are few specific data for VCI.[11]

Physical activity has beneficial effects on synaptogenesis, neurogenesis, and vascular health and might, therefore, reduce the risk of cognitive impairment. Indeed, observational studies suggest a beneficial influence on risk of cognitive decline, VaD, AD, and dementia in general.[11] A beneficial effect of physical activity on cognitive function is further suggested by randomized trials in patients at risk for AD[250] and by multicomponent interventions that included physical activity.[239]

Overweight and obesity are important risk factors for cognitive decline and dementia in general. However, disentangling the specific influence of obesity from the influence of insulin resistance and other components of the metabolic syndrome on cognitive decline is difficult. Also, there is no interventional study that examined the effect of weight reduction on the risk of cognitive decline.[11]

Vascular Risk Factors and Concomitant Vascular Disease

The efficacy of blood pressure (BP) lowering to prevent cognitive impairment in the elderly beyond stroke prevention is still controversial.[3] This in part relates to methodological limitations shared by BP-lowering trials.[11] However, in light of the documented benefit of BP-lowering therapy on vascular outcomes, it is recommended to treat hypertension in people at risk for VCI.[3]

The level of evidence that treating diabetes mellitus and hyperglycemia reduces the risk of VCI and dementia in general is likewise low,[11,251,252] but the benefit on multiple target organs (heart, eye, and kidney) is important enough to recommend strict glycemic control. Also, glycemic control has been shown to restore deficits in cerebral perfusion in diabetic

Table 2. Risk Factors for VCI

Risk Factors	Strength of Evidence*	References
Nonmodifiable		
Age	Strong	Pendlebury and Rothwell[103], Leys et al[185], Allan et al[190], Narasimhalu et al[191], Yang et al[198], Kalaria et al[235]
Female sex	Some evidence for PSD	Pendlebury and Rothwell[103]
Genetic factors	Weak (few specific risk genes known)	Haffner et al[110], Schrijvers et al[236]
Modifiable		
Education	Some evidence	Dichgans and Zietemann[11], Zieren et al[50], Kalaria et al[235]
Smoking	Some evidence	Dichgans and Zietemann[11], Anstey et al[237], Rusanen et al[238]
Physical activity	Some evidence	Ngandu et al[239], Aarsland et al[240]
Obesity and body mass index	Some evidence	Gorelick et al[3], Dichgans and Zietemann[11], Anstey et al[241]
Hypertension	Strong for hypertension in midlife	Dichgans and Zietemann[11], Skoog et al[242], Kivipelto et al[243], Iadecola et al[244]
Chronic hyperglycemia, diabetes mellitus	Strong	Gorelick et al[3], Dichgans and Zietemann[11], Yang et al[198], Cosentino et al[245], Panza et al[246], Zietemann et al[247]
Lipids, dyslipidemia	Some evidence for total cholesterol levels in midlife	Gorelick et al[3], Dichgans and Zietemann[11], Solomon et al[248]

PSD indicates poststroke dementia; VaD, vascular dementia; and VCI, vascular cognitive impairment.
*In some cases, the relationship has been established for VaD but not for VCI in general.

patients.[245] From the 2 statin trials that evaluated cognition as a secondary end point, there is no evidence that statin treatment reduces the risk of cognitive decline or incident dementia. However, these studies were not powered to answer the question, and follow-up may have been too short.[253,254]

Based on observational data, prevention of concomitant vascular disease in particular coronary artery disease, chronic heart failure, or chronic kidney disease is a reasonable strategy to prevent VCI.[3] Yet, there are few data from randomized controlled trials to support this.

Cerebrovascular Disease

Few trials on primary or secondary stroke prevention provided cognitive end points. The SPS3 trial (Secondary Prevention of Small Subcortical Strokes) had a 2-by-2 factorial design and compared the effect of dual antiplatelet treatment versus single aspirin and intensive BP lowering versus usual targets in patients with small subcortical infarcts. There was no significant treatment effect on cognitive end points with either dual antiplatelet therapy or intensive BP lowering.[203] The PRoFESS trial (Prevention Regimen for Effectively Avoiding Second Strokes), which included patients with ischemic stroke, found no benefit of 25 mg of aspirin plus 200 mg of extended-release dipyridamole twice daily for risk of cognitive decline or dementia compared with 75 mg of clopidogrel once a day.[202] However, follow-up in these trials may have been too short for an effect on cognition. In the PROGRESS trial (Perindopril Protection Against Recurrent Stroke Study), treatment with 4 mg of perindopril daily showed a reduction in the risk of dementia in the subgroup of patients with a prior history of stroke when compared with placebo.[255] Active treatment further stopped or delayed the progression of WMH.[256]

Whether patients with SBI or extensive WMH but without a history of stroke benefit from antiplatelet or BP-lowering therapy is currently unknown, and current guidelines and expert statements provide no recommendations on how to treat these patients.[3]

Multicomponent Interventions

Multicomponent interventions take a comprehensive approach by targeting multiple risk factors and domains in parallel. The ASPIS trial (Austrian Polyintervention Study to Prevent Cognitive Decline After Ischemic Stroke)[257] found no benefit of a multicomponent intervention that focused on lifestyle and vascular risk factors, compared with standard care in patients with stroke. However, sample size was small and follow-up was only 2 years. The FINGER trial (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability)[239] recruited 1260 at-risk individuals aged 60 to 77 years, randomly assigned to either a 2-year course of multidomain intervention (nutritional advice, exercise, cognitive training, and vascular risk monitoring) or general health advice. Subjects randomized to the multidomain intervention had better cognitive outcomes than controls. Additional trials are currently ongoing.

Treatment

General management principles for VCI are those of MCI and dementia and include the treatment of comorbidities, including psychological and behavioral symptoms, providing information and support to the patient and caregivers and maximizing independence.[3,18] The observed modest effect of symptomatic treatment in patients with AD together with preclinical results and pathological evidence for a cholinergic deficit in VCI[258] has prompted randomized controlled trials with choline esterase inhibitors and memantine in patients with VaD. Two trials with galantamine showed no significant treatment benefit for clinician's global impression of change, activities of daily living, and neuropsychiatric symptoms.[259,260] However, there was a significant benefit for cognition in one of the trials.[260] Among the 3 trials conducted with donepezil, all found a significant

benefit for cognition,[261–263] while only 1 showed a significant global benefit,[262] and only 1 showed a benefit for activities of daily living.[261] Donepezil was further tested in 168 patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, who had cognitive impairment, and found to have no effect on the primary cognitive end point. However, improvements were noted on several measures of executive function.[264] In the single trial of rivastigmine, there was a significant benefit on the cognition without significant global benefit or benefit on activities of daily living.[265] And the same was seen in 2 studies with the *N*-methyl D-aspartate antagonist memantine. Despite the small effect on cognition, some experts recommend considering donepezil for cognitive enhancement in patients with VaD.[3]

Conclusion

Recent work has led to a substantially improved understanding on how vascular brain injury affects cognition. However, more work is required to disentangle the effects of vascular factors and neurodegenerative disease. Preventing vascular injury remains a promising approach to reduce the global burden of dementia, but additional efforts are needed to define the optimal strategy for prevention and develop efficient symptomatic treatments.

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Disclosures

None.

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