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Vascular Cognitive Impairment and Dementia

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Abstract

PURPOSE OF REVIEW: This article gives a broad overview of vascular cognitive impairment and dementia, including epidemiology, pathophysiology, clinical approach, and management. Emphasis is placed on understanding the common underlying types of cerebrovascular disease (including atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy) and awareness of rare inherited cerebrovascular disorders.

RECENT FINDINGS: The pathophysiology of vascular cognitive impairment and dementia is heterogeneous, and the most recent diagnostic criteria for vascular cognitive impairment and dementia break down the diagnosis of major vascular dementia into four phenotypic categories, including subcortical ischemic vascular dementia, poststroke dementia, multi-infarct dementia, and mixed dementia. Control of cardiovascular risk factors, including management of midlife blood pressure, cholesterol, and blood sugars, remains the mainstay of prevention for vascular cognitive impairment and dementia. Cerebral amyloid angiopathy requires special consideration when it comes to risk factor management given the increased risk of spontaneous intracerebral hemorrhage. Recent trials suggest some improvement in global cognitive function in patients with vascular cognitive impairment and dementia with targeted cognitive rehabilitation.

SUMMARY: Thorough clinical evaluation and neuroimaging form the basis for diagnosis. As vascular cognitive impairment and dementia is the leading nondegenerative cause of dementia, identifying risk factors and optimizing their management is paramount. Once vascular brain injury has occurred, symptomatic management should be offered and secondary prevention pursued.

INTRODUCTION

Dementia is defined as a decline in cognitive function causing impairment that interferes with independence in everyday activities.[1] Vascular cognitive impairment and dementia refers to cognitive impairment or dementia that results from vascular brain injury. Vascular brain injury refers to damage to brain parenchyma resulting most commonly from ischemia, infarction, and hemorrhage.

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Drs Wong and Chui discuss the unlabeled/investigational use of donepezil for the treatment of vascular cognitive impairment and dementia and mixed vascular cognitive impairment and dementia/Alzheimer disease.

Vascular cognitive impairment and dementia are among the most common causes of dementia after Alzheimer disease (AD).[2] The most common risk factors for vascular cognitive impairment and dementia are cardiovascular risk factors, including hypertension, hyperlipidemia, type 2 diabetes mellitus, smoking, and atrial fibrillation.

The first description of what may be thought of as classic vascular dementia, with stepwise decline and hemiplegia, can be traced back as far as 1672.[3] Since then, advances through autopsy evaluations and improvements in imaging techniques have broadened insight into the vascular changes that cause what is now described as vascular cognitive impairment and dementia.[4] The terminology surrounding vascular cognitive impairment and dementia has evolved over time, even within the past 50 years, shifting from the umbrella term *multi-infarct dementia*[5] to more nuanced understandings of the contributions of cerebrovascular disease to cognitive impairment as discussed in this article. This article explores vascular brain injury as it relates to and serves as a precursor for vascular cognitive impairment and ultimately vascular dementia and discusses the most recent evidence regarding epidemiology, pathophysiology, clinical approach, and management of vascular cognitive impairment and dementia.

EPIDEMIOLOGY OF VASCULAR COGNITIVE IMPAIRMENT AND DEMENTIA

Vascular dementia is traditionally thought to be the second most common cause of dementia in the United States, comprising approximately 15% to 20% of clinically diagnosed dementia cases in North America and Europe.[4] In Asia and some developing countries, the estimated burden of vascular dementia is thought to be closer to 30%,[6,7] and as such, it may be the leading cause of dementia in those countries. The picture becomes more complex when neuropathologic changes form the basis of diagnosis. In some neuropathologic studies, mixed vascular and Alzheimer pathology has been found to have a prevalence of 20% to 27%,[8–12] whereas others have shown a prevalence of up to 38%, with pure vascular pathology seen only in 12%.[13] The probability of mixed dementia increases with increasing age, and the combination of multiple pathologies has been shown to be significantly correlated with the risk of clinical dementia.[12–15] In the Rush Religious Orders Study and Rush Memory and Aging Project, neuropathologic evidence of vascular disease alone or in combination with AD was present in a plurality of cases across the spectrum of cognitive impairment, from none to major.[14] However, an increasing prominence of Alzheimer pathology strongly aligns with increasing severity of cognitive impairment and dementia (FIGURE 5-1). It should be noted that cerebral amyloid angiopathy (CAA) can cause vascular brain injury as well.

PATHOGENESIS OF VASCULAR COGNITIVE IMPAIRMENT AND DEMENTIA

The pathogenesis of vascular cognitive impairment and dementia may be proposed as follows: vascular risk factors lead to cerebrovascular disease that results in vascular brain injury, and disruption of cognitive networks due to vascular brain injury leads to vascular cognitive impairment and dementia (FIGURE 5-2). The best treatment of vascular cognitive impairment and dementia is through prevention by detecting and mitigating vascular risk factors as early in life as possible.

Vascular Risk Factors

Cardiovascular risk factors increase the relative risk of dementia, which can be modified by early implementation of lifestyle changes and medications.[16] For example, nearly 10% of the weighted population attributable risk for dementia is accounted for by four vascular risk factors: smoking (5.2%), hypertension (1.9%), diabetes mellitus (1.2%), and physical inactivity (1.6%). The prevalence of cardiovascular risk factors may differ significantly based on race. In the Atherosclerosis Risk in Communities Study, the prevalence of hypertension (56% versus 27%) and type 2 diabetes mellitus (18% versus 7%) was twice as high among Black people than White people.[17,18] However, the strengths of association between the severity of cardiovascular risk factors and resulting vascular brain injury or vascular cognitive impairment and dementia were similar across the two racial groups. Similar correlations were found between systolic blood pressure and volume of white matter hyperintensities[19] and between baseline hemoglobin A_{1c} and subsequent cognitive decline.[20] These findings suggest that disparities in the prevalence of risk factors may be related to social determinants of health more than race and that management of risk factors is equally important across racial groups. For more information on health disparities and social determinants of health, refer to the article “Health Disparities in Dementia” by Joyce (Joy) E. Balls-Berry, PhD, MPE, and Ganesh M. Babulal, PhD, OTD, MSCI, MOT, in this issue of *Continuum*.[21]

APOE ε4 predisposes to the accumulation of amyloid-β in cerebral blood vessels (resulting in CAA) as well as in the brain parenchyma (amyloid plaques) and is another risk factor for vascular brain injury, but it is not a risk factor for coronary artery disease. Thus, when enumerating cerebrovascular risk factors, one must think beyond traditional cardiovascular risk factors.

Major Types of Cerebrovascular Disease

Many types of cerebrovascular diseases contribute to vascular cognitive impairment and dementia (FIGURE 5-3),[22] but only the major types are discussed in this article. Specific cardiovascular risk factors and types of cerebrovascular disease show predilections for certain parts of the vascular tree (eg, large arteries, small arteries, veins, or capillaries) and are described below. These generalizations are helpful in differential diagnosis but should be considered only as general guidelines. Neuropathologic studies illustrate how various types of cerebrovascular disease often coexist and can affect multiple sites in the vascular tree.[23] The past several decades have witnessed significant advances in our ability to detect vascular brain injury and the presence of cerebrovascular disease on structural and susceptibility-weighted imaging (SWI) studies.

ATHEROSCLEROSIS.—Atherosclerosis affects the intimal lining of large feeding arteries (eg, aorta; carotid arteries; vertebral arteries; and the pial vessels of the anterior, middle, and posterior cerebral arteries). Major risk factors for atherosclerosis include smoking and hyperlipidemia. Occlusion of large arteries by thrombosis or cardioembolism leads to wedge-shaped infarcts affecting both cortical gray and underlying subcortical white matter, thereby disrupting widespread components of multiple brain networks, resulting in stepwise functional decline and the well-recognized syndromes of multi-infarct dementia

or poststroke dementia. On the other hand, artery-to-artery emboli can also result in small cortical microinfarcts, which can only be visualized with high-field MRI or postmortem.

ARTERIOLOSCLEROSIS.—Arteriolosclerosis affects the medial smooth muscle wall of small cortical and penetrating arterioles that feed the basal ganglia and deep white matter. Hypertension is the major risk factor for arteriolosclerosis. Occlusion of small arteries leads to lacunar infarcts as well as central hemorrhages and microbleeds. Widespread stenosis of the long penetrating arterioles leads to chronic ischemia of the periventricular and deep white matter, visualized as white matter hyperintensities on MRI and white matter changes that appear hypodense on CT. Lacunar infarcts and white matter hyperintensities can often be strategically located to disrupt frontal-subcortical circuits and cause impairments in executive function, recognized as the syndrome of subcortical ischemic vascular dementia or small vessel disease, described later in this article.

CEREBRAL AMYLOID ANGIOPATHY.—CAA involves buildup of amyloid-β predominantly affecting pial and cortical arteries as well as capillaries, with relative sparing of the penetrating arterioles that supply the basal ganglia (striatum and thalamus). Consensus is lacking as to whether to classify AD with CAA-related vascular brain injury as pure AD or mixed AD/vascular cognitive impairment and dementia; in this article, *APOE* ε4 and CAA are considered as risk factors for vascular cognitive impairment and dementia. The *APOE* ε4 genotype is the major risk factor for CAA. CAA is associated with lobar hemorrhages (large and small), cortical microinfarcts, and white matter hyperintensities. Although these vascular brain injury hallmarks can be detected by MRI and form the basis for a clinical diagnosis of CAA, definitive diagnosis of CAA is based on autopsy findings.

MICROVASCULAR DISEASE.—Microvascular disease involves the tissue-level delivery of fuel/nutrients and clearing of metabolic waste products that occurs at the capillary neurovascular unit (FIGURE 5-4).[24–27] Type 2 diabetes mellitus is among the most common risk factors for microvascular disease. Studies by Moran and colleagues[28] show that type 2 diabetes mellitus is associated with cerebral atrophy.

Regional assessment of the blood-brain barrier using dynamic contrast enhancement has been a relatively recent development.[29] Increased K_{trans}, a measure of leakage of gadolinium contrast from blood to brain, has been demonstrated in carriers of the *APOE* ε4 genotype[30,31] and persons with confluent subcortical leukoencephalopathy.[32,33]

Evidence From Neuropathology

Neuropathologic studies illustrate a high degree of heterogeneity in the types of cerebrovascular disease and vascular brain injury and their overlap with AD pathology. In a study of patients diagnosed clinically with probable AD, 21% of participants were found to have cerebrovascular disease without AD pathology, with about 50% of these participants having both infarcts (micro and macro) and vessel disease (including atherosclerosis, arteriolosclerosis, and CAA).[14] Another study of neuropathologic correlates in a population-based study showed that among participants with dementia, 42% had cerebral infarcts, 46% had cortical microvascular lesions, 38% had subcortical microvascular lesions, and 42% had

some amount of CAA, although the proportion of participants with overlaps in pathology was not explicitly stated.[34]

A large combined autopsy series from the Rush Religious Orders Study, Rush Memory and Aging Project, and the Minority Aging Research Study (n = 1474) examined the frequency of the major types and combinations of cerebrovascular disease and their associations with longitudinal cognitive decline (FIGURE 5-5).[35] Pure arteriolosclerosis and atherosclerosis without brain tissue injury (defined as macroinfarcts or microinfarcts) were associated with little overall decline in domain-specific cognitive function, whereas CAA was associated with decline in semantic memory and visuospatial ability. On the other hand, mixed types of vascular disease (eg, various combinations of arteriolosclerosis, atherosclerosis, and CAA) were strongly associated with cognitive decline ($\beta = -0.03$, standard error = .007, $P<.001$), more so if evidence existed of vascular brain injury.

LARGE-SCALE COGNITIVE AND BEHAVIORAL NETWORKS

With the advent of structural and functional neuroimaging, significant advances have been made in delineating large-scale human brain networks.[36] Network-sensitive neuroimaging methods have shown how different neurodegenerative syndromes (eg, Alzheimer dementia, semantic dementia, and behavioral variant frontotemporal dementia) cause circumscribed atrophy within distinct intrinsic functional connectivity networks for memory, language, and behavior.[37] Similar network analyses elucidate how vascular brain injury disrupts brain networks (eg, cognitive control, default mode, salience networks), resulting in cognitive and behavioral changes following stroke (eg, executive dysfunction,[38] depression, and apathy[39]).

The anatomic signature of vascular brain injury is highly heterogeneous, although patterns are discernable. For example, fluent and nonfluent aphasia are associated with infarctions in the territory of the left middle cerebral artery. Impairment of executive function is commonly associated with subcortical lacunar infarcts and confluent white matter changes.

A series of parallel frontal-subcortical anatomic circuits are important in modulating behavior.[40] The dorsolateral prefrontal circuit regulates central executive control, including anticipating, planning, and monitoring performance. Disruption along this pathway may result in impairments of cognitive testing, including poor attention and set shifting consistent with dysexecutive function. Two of the frontal-subcortical circuits mediate behavior: the anterior cingulate circuit mediates motivation (CASE 5-1), and the orbitofrontal circuit is involved in the salience network and mediates inhibition.

CLINICAL APPROACH

The mainstay of the clinical approach to vascular cognitive impairment and dementia remains the history and physical/neurologic (including mental status) examination. Imaging lends significant sensitivity and specificity to the etiologic diagnosis. The location of vascular brain injury goes a long way in explaining signs and symptoms. Vascular risk factors and subtype of cerebrovascular disease are especially relevant for designing primary and secondary prevention strategies.

Clinical History

As with all neurologic disorders, obtaining a careful history can provide significant insight into the cause of the disease. For neurocognitive disorders, understanding the initial presenting symptom is key to diagnosis, and the same holds true for diagnosing vascular cognitive impairment and dementia. As Alzheimer disease and vascular cognitive impairment and dementia are among the top two causes of dementia, a quick reference for distinguishing key aspects of the two is provided in TABLE 5-1.

A past medical history of multiple cardiovascular risk factors and a surgical history of cardiac surgeries or procedures for peripheral vascular disease may raise concern for vascular brain injury. Initial cognitive symptoms of subtle changes in executive function and attention rather than memory impairment would be expected in subcortical ischemic vascular dementia. A chief complaint of sudden onset of cognitive changes in conjunction with symptoms of a stroke would be consistent with poststroke dementia. A family history of dementia may be uncovered, particularly in the presence of cardiovascular risk factors. Social history may reveal many pack-years of smoking. Although neuroimaging is helpful in seeing evidence of vascular brain injury suggestive of the diagnosis of vascular cognitive impairment and dementia, it may not always be available or reliable, and the importance of the history should not be overlooked.

Physical and Neurologic Examination

When evaluating for vascular cognitive impairment and dementia, a careful physical examination can reveal many significant findings related to cardiovascular risk factors. Funduscopic examination may reveal hypertensive retinopathy. Examination of the extremities, particularly the legs, may reveal the skin changes of peripheral vascular disease or pitting edema from heart failure. A thorough cardiopulmonary examination may reveal an irregular rhythm concerning for atrial fibrillation, a carotid bruit indicating large vessel plaque buildup, or crackles from fluid overload due to heart failure.

Neurologic findings can vary widely from focal neurologic deficits consistent with stroke (eg, facial droop, visual field cut, hemiplegia, hemisensory loss) to evidence of peripheral neuropathy indicating poorly controlled diabetes. Parkinsonism due to vascular brain injury may mimic idiopathic Parkinson disease, with bradykinesia, gait disturbance, and rigidity.

Cognitive Examination

The pattern of cognitive impairment in vascular cognitive impairment and dementia can vary widely depending upon the location of vascular brain injury. The VICCCS (Vascular Impairment of Cognition Classification Consensus Study) criteria delineated four phenotypic subgroups, as discussed below (FIGURE 5-7).[40]

SUBCORTICAL ISCHEMIC VASCULAR DEMENTIA.—Typically with subcortical ischemic vascular dementia, one would expect indolent progression of dysexecutive function and decline in speed of information processing or complex attention. In a study comparing the Montreal Cognitive Assessment (MoCA) to the Mini-Mental State Examination (MMSE), the MoCA was shown to capture deficits due to vascular brain injury more often

than the MMSE given its more robust measures of executive dysfunction.[42] In a study by Ramirez-Gomez and colleagues,[43] a modest positive likelihood ratio in distinguishing subcortical ischemic vascular dementia versus Alzheimer dementia was seen such that patients with autopsy-confirmed AD showed greater impairment in delayed recall and category (compared to phonemic) fluency.

POSTSTROKE DEMENTIA.—Patients with a history of stroke may have predominant language or memory difficulties, depending on the location of the stroke. To characterize vascular cognitive impairment and dementia as poststroke dementia by VICCCS criteria, these deficits must be present either immediately after or within 6 months of stroke and do not recover.[41] In particular, the regions identified by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria with the greatest effect on cognition include the angular gyrus, thalamus, basal forebrain, basal ganglia, posterior cerebral artery territories (including the hippocampus) (CASE 5-2), and anterior cerebral artery territories.[44] Associations between infarct location and impairment of cognitive domains have recently been examined using assumption-free support vector regression. The left angular gyrus, the left basal ganglia, and the white matter around the left basal ganglia emerged as strategic structures for global cognitive impairment. This methodologic approach also identified domain-specific cortical and subcortical structures (FIGURE 5-8).[45]

MULTI-INFARCT DEMENTIA.—Multi-infarct dementia as defined by the VICCCS criteria refers to the involvement of multiple large cortical infarcts in the development of vascular cognitive impairment and dementia, and cognitive evaluation may reveal cortical signs such as apraxia, aphasia, visual field cut, or neglect.

MIXED DEMENTIA.—The most common dementia mixed with vascular cognitive impairment and dementia is AD,[13] although combinations with other neurodegenerative diseases are possible. The cognitive profile of patients with vascular cognitive impairment and dementia/AD may look very similar to that of patients with pure AD, with a primarily amnestic syndrome; however, imaging characteristics or biomarkers may distinguish the two.

Neuroimaging

Advances in neuroimaging have changed the landscape of diagnosis in neurology, and vascular cognitive impairment and dementia is no different. MRI and CT are the most commonly used imaging modalities to evaluate for vascular brain injury, but newly discovered tracers for PET imaging have been helpful in ruling in or out other neurodegenerative causes of dementia.

MRI.—MRI of the brain without contrast can provide comprehensive information, with different sequences and orientations providing valuable insight in the evaluation of cognitive impairment.

T1-WEIGHTED SEQUENCE.: The T1-weighted sequence is best for evaluating brain anatomy and regional patterns of atrophy. Thinning of the corpus callosum on sagittal views is associated with white matter ischemia. A coronal T1-weighted sequence is best for assessment of hippocampal atrophy. Hippocampal atrophy is prominent in AD and limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy (LATE), whereas hippocampal volume is relatively preserved in pure vascular cognitive impairment and dementia. Note that generalized cerebral atrophy is not specific and can be associated with cardiovascular risk factors[46] and cerebrovascular disease as well as neurodegenerative disorders.[47]

T2-WEIGHTED/FLUID-ATTENUATED INVERSION RECOVERY SEQUENCES.: Abnormal white matter changes appear bright on both T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences. However, FLAIR is better than T2-weighted sequences in distinguishing lacunar infarcts from dilated perivascular spaces. On FLAIR, lacunar infarcts appear as areas of encephalomalacia surrounded by hyperintensity, whereas both dilated perivascular spaces and lacunar infarcts are bright on T2-weighted images. The degree of white matter changes can be classified based on the Fazekas scale (FIGURE 5-10[48]), which classifies periventricular and deep white matter abnormalities into grades 0 to 3, corresponding to absent, mild, moderate, and severe changes (TABLE 5-2[49]).[50] Severe white matter disease strongly predicted rapid global functional decline in participants in the LADIS (Leukoaraiosis and Disability Study) cohort.[48] Of note, white matter changes associated with CAA can be virtually indistinguishable from those caused by cardiovascular risk factors, making clinical history particularly important in the diagnosis.

GRADIENT RECALLED ECHO AND SUSCEPTIBILITY-WEIGHTED IMAGING.: Gradient recalled echo (GRE), SWI sequences, or any sequence sensitive to differences in tissue susceptibility or iron/blood products, are ideal for evaluating for the presence of microbleeds, which appear as blooming artifacts (lesions with hemosiderin deposition that appear larger on MRI than they are in reality). Microbleeds found in deep subcortical structures are more consistent with hypertensive etiology, whereas lobar microbleeds at the gray-white junction, blood within the subarachnoid space, and superficial siderosis (hemosiderin deposition along superficial layers of the cerebral cortex) are suggestive of CAA (FIGURE 5-11[51]).

DIFFUSION-WEIGHTED IMAGING.: Diffusion-weighted imaging should be reviewed to assess for the presence of acute stroke, particularly given the high burden of cardiovascular risk factors in patients with vascular cognitive impairment and dementia.

CT.—CT of the head is an option if the patient is unable to tolerate MRI, whether because of behavioral issues (eg, patient is easily frightened/agitated or unable to hold still) or metallic implants (eg, MRI-incompatible pacemaker) but has the disadvantages of being lower in resolution and exposing the patient to radiation. CT allows for a gross evaluation of intracranial lesions, parenchymal atrophy, and ventricular size, which is helpful for ruling out other causes of cognitive impairment. It is most helpful for evaluation of macrohemorrhages; microbleeds are not visible on CT. Encephalomalacia related to prior

stroke is often easily appreciated on CT as well. Although white matter disease can be appreciated as hypodensity on CT, it is not as clearly distinguished from normal white matter (which is also relatively hypodense on CT) as it is on MRI.

VESSEL IMAGING.—Magnetic resonance angiography (MRA) of the head and neck is valuable to assess the amount of atherosclerotic disease present and does not require contrast injection to be meaningful. Medical management may differ based on the presence of intracranial atherosclerosis,[52] and surgical intervention may be warranted for severe or symptomatic carotid stenosis.[53] CT angiography of the head and neck offers similar information with greater specificity and sensitivity than MRA of the head and neck[54] but at the cost of additional radiation and potential toxicity from iodine-based contrast. Carotid duplex ultrasound is an alternative for assessment of the carotid arteries, and transcranial Doppler is an alternative for assessment of the large intracranial vessels; these methods can reliably predict the presence of carotid[55] and intracranial stenosis.[56]

FLUDEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY.—In vascular dementia, fludeoxyglucose positron emission tomography (FDG-PET) may show decreased glucose uptake reflecting hypometabolism in focal cortical, subcortical, deep gray nuclei, and cerebellar regions[57] related to locations of prior stroke or regions functionally connected to prior stroke. FDG-PET is particularly helpful as a means of showing the typical temporal-parietal-frontal signature of AD to rule in (or out) mixed vascular cognitive impairment and dementia/AD.

AMYLOID POSITRON EMISSION TOMOGRAPHY.—Amyloid-β–specific PET allows for the detection of fibrillar amyloid-β to detect AD pathology in vivo. An amyloid PET scan is helpful in assessing for mixed vascular cognitive impairment and dementia/AD/CAA. Although approved by the US Food and Drug Administration (FDA), amyloid PET scans are only reimbursed by the US Centers for Medicare & Medicaid Services at the present time under limited “coverage with evidence development.” It is important to bear in mind that amyloid positivity increases with age and may be present in 20% of cognitively asymptomatic persons older than 80 years of age.[58] Thus, amyloid PET scans are clinically available but not commonly used in clinical practice because they must generally be paid for out of pocket.

Diagnostic Criteria

Multiple diagnostic criteria have been proposed over the past 3 decades, with the most recent iteration by the VICCCS in 2017.[41] Before the VICCCS criteria, other criteria had been developed,[4,44,59] which generally included clinical signs of either acute stroke or cognitive impairment in the domains related to frontal-subcortical loops or other cognitive networks, neuroimaging evidence of vascular disease, and exclusion of other causes of cognitive impairment (including other medical, psychiatric, or neurodegenerative diseases).

Given the high prevalence of mixed and heterogeneous pathology when it comes to vascular dementia, it should be noted that proposed criteria tend to be more specific than they are sensitive[60–62] and that different criteria yield different prevalence rates for vascular cognitive

impairment and dementia.[63,64] The NINDS-AIREN criteria from 1994 were developed to identify pure cases of vascular dementia for research studies and as such are still among the most specific.[44,65] The role of fluid biomarkers may become another important consideration in diagnostic criteria in the future.

OTHER CONSIDERATIONS

The most common cause of vascular cognitive impairment and dementia is poorly controlled cardiovascular risk factors. However, vascular cognitive impairment and dementia can also be caused by mixed dementia (as described above), CAA, or genetic mutations.

Cerebral Amyloid Angiopathy

CAA is associated with Alzheimer pathology (that is, amyloid-β plaques and phosphorylated tau neurofibrillary tangles), *APOE* ε4, and vascular brain injury.[66] CAA has distinct signatures on neuroimaging, as described above. The distinguishing clinical history with vascular cognitive impairment and dementia caused by CAA includes slowly progressive cognitive decline (as would be seen in Alzheimer dementia), episodic transient focal neurologic episodes (so-called amyloid spells, CASE 5-3), and sudden-onset focal neurologic deficits secondary to cortical lobar intracerebral hemorrhages (ICH).[67] Clinically, the distinction between vascular cognitive impairment and dementia caused by CAA as opposed to arteriolosclerosis has important implications for clinical management. For example, amyloid spells may be difficult to clinically distinguish from transient ischemic attacks, but treatment with antithrombotics may increase the risk of ICH.[68]

Genetic Mutations

A host of genes, both monogenic and polygenic, have been associated with small vessel disease (TABLE 5-3),[69] with the most common being cerebral autosomal dominant/recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL/CARASIL). CADASIL is associated with autosomal dominant mutations in the *NOTCH3* gene, whereas CARASIL results from an autosomal recessive mutation in the *HTRA1 g*ene.[69] Both are associated with ischemic stroke and confluent white matter hyperintensities. Although the classic phenotype for CADASIL and CARASIL includes onset between the ages of 20 to 50 with migraines and multiple strokes, some patients may present with seizure,[70] and variants of CADASIL have been identified that present primarily with subcortical vascular cognitive impairment with a median age of 74 (CASE 5-4).[71] A strong family history of vascular cognitive impairment and dementia without significant cardiovascular risk factors may be suggestive of this entity, which is important to identify given its implications for future generations.

MANAGEMENT

The ideal management for vascular cognitive impairment and dementia is prevention through effective control of cardiovascular risk factors. Of the acquired dementias, vascular dementia, when not complicated by mixed dementia, CAA, or genetic mutations, is unique in that it has known modifiable risk factors and may, in fact, be nondegenerative if those risk

factors are well controlled. Unfortunately, none of the interventions discussed below have been shown to improve cognition in patients who already show cognitive impairment.[72]

Primary Prevention

In 2017, the American Heart Association/American Stroke Association released an advisory to define optimal brain health, derived from the American Heart Association's Life's Simple 7.[73] Optimal brain health is defined by seven metrics, including ideal health behaviors and factors, which together have been shown to play a role in the preservation of cognition.[74] Specific recommendations for these metrics can be found in TABLE 5-4.[75] Additionally, pursuing cognitively and socially stimulating and rewarding activities and addressing mental health concerns are important to maintaining brain health.[73]

Secondary Prevention

Appropriate secondary prevention for vascular cognitive impairment and dementia can theoretically halt the progression of cognitive impairment. Special consideration should be given for cases involving CAA, as described below.

BLOOD PRESSURE.—Elevated blood pressure in midlife is associated with increased incidence of dementia and thus constitutes a modifiable risk factor, particularly for vascular cognitive impairment and dementia. Although no particular antihypertensive drug class has been shown to consistently reduce the risk of cognitive decline or dementia,[76] some studies have suggested that angiotensin-converting enzyme (ACE) inhibitors may protect against vascular cognitive impairment and dementia.[77]

Although the SPRINT (Systolic Blood Pressure Intervention Trial) study showed that intensive blood pressure control (systolic blood pressure <120 mm Hg) was more effective in reducing cardiovascular outcomes and all-cause mortality than standard blood pressure control (systolic blood pressure <140 mm Hg),[78] no clinically relevant difference was seen in memory or processing speed.[79]

In patients older than 80 years of age, the American Society of Hypertension recommends blood pressure goals of less than 150/90 mm Hg to reduce cardiovascular and stroke risk.[80] Notably, the Leiden 85-plus Study, a cohort study of participants older than 85 years of age, found that lower systolic blood pressure in participants who were on antihypertensives was associated with higher mortality and faster cognitive decline, with an annual change in MMSE of −0.35 per 10 mm Hg drop in systolic blood pressure.[81] Thus, in late life or in people with significant confluent white matter hyperintensities (Fazekas scale grade 3) due to arteriolosclerosis, it seems prudent to maintain systolic blood pressure in the 120 mm Hg to 140 mm Hg range. However, in patients with a diagnosis of CAA, blood pressure should ideally be maintained at less than 120/80 mm Hg, as even slightly elevated blood pressures have been associated with increased risk of ICH.[82]

LIPIDS.—The relationship between serum total cholesterol and dementia is complicated and appears to differ in middle and late life. Midlife high serum total cholesterol is a risk factor for subsequent dementia/Alzheimer disease, but a decline in levels of

cholesterol after midlife may reflect many factors (including ongoing disease processes) and may be associated with increased cognitive impairment in late life.[83,84] To complicate matters further, U-shaped associations have been described between the level of non-HDL cholesterol and increasing cognitive impairment, with stronger associations with both higher and lower cholesterol levels.[85] Statins are a mainstay in cardiovascular risk factor management, and some studies have shown slower rates of cognitive decline and potential reduction in dementia in patients using statins.[80] The effects of statins among persons with mild cognitive impairment or AD, or in older people without cognitive impairment, is less well studied. In 2012, the FDA updated the safety label for statins to include concern for "not serious and reversible" cognitive side effects, while maintaining that the cardiovascular benefits outweigh the small potential risk.[86] This brought to surface years of controversial concerns about statins' effect on cognition, and since then, many publications have emerged for further exploration. Concerns that decreasing low-density lipoprotein cholesterol (LDL-C) levels may result in more cognitive impairment have been addressed by the large-scale EBBINGHAUS (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects) study published in 2017 on the use of proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) inhibitors in addition to statin therapy, which showed no difference in cognitive function between participants with lowest-attained LDL-C of less than 25 mg/dL, between 25 mg/dL and 30 mg/dL, or greater than 40 mg/dL over the study period of 19 months.[85] An even more recent study by Hua and colleagues[88] showed that in a US population-based study of individuals older than 50 years of age, low LDL-C levels (less than 70 mg/dL) were associated with significantly slower 2-year rates of decline in global cognitive function. A systematic review by Richardson and colleagues[89] suggested that the adverse event reporting rates for cognitive impairment with statins is similar to that of other commonly used medications, and meta-analysis showed that statin use was associated with a 13% relative risk reduction for all-cause dementia. Based on these results, no strong evidence suggests that statins should be discontinued or avoided for concern of cognitive impairment, and rather, the known cardiovascular benefit of statin use argues in favor of continued statin use and LDL-C reduction for secondary prevention. In unique cases, for patients on statins with prominent cognitive symptoms for whom no other cause of cognitive impairment is identified, a trial of statin discontinuation can be considered. If cognitive symptoms improve in this population, given that lipophilic statins (eg, atorvastatin, simvastatin) may have higher reports of cognitive side effects than hydrophilic statins (eg, rosuvastatin, pravastatin), choosing to reinitiate a hydrophilic statin for cardiovascular and cerebrovascular protection is reasonable.[90]

Some studies have shown increased risk of ICH with the use of statins,[91] possibly related to their effects on coagulation and fibrinolysis.[92] This poses a particular problem for patients with CAA, who are already at increased risk for ICH; however, current recommendations are to continue the use of statins in patients for which its use is indicated per American College of Cardiology/American Heart Association guidelines.[68]

BLOOD SUGAR.—Although poor glycemic control has been found to correlate with worse cognitive function,[93] episodes of hypoglycemia have also been associated with increased risk of dementia.[94] In particular, the ADVANCE (Action in Diabetes and

Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial evaluated participants with mean age of 66 and found that intensive diabetes control (mean hemoglobin A_{1c} <6.5%) was associated with higher rates of dementia compared to a standard control group (hemoglobin A_{1c} <7.3%).[95] In the ACCORD MIND (Action to Control Cardiovascular Risk in Diabetes: Memory in Diabetes) study, which included participants 55 to 80 years of age, intensive glycemic treatment (hemoglobin A_{1c} <6.0%) was associated with increased mortality compared to standard treatment (hemoglobin A1c of 7.0% to 7.9%) but no difference in cognitive outcomes.[96] These findings do not support intensive glycemic control beyond midlife, and suggest a goal hemoglobin A_{1c} of 7.0% to 7.9% is reasonable.

ANTITHROMBOTIC MEDICATIONS.—Often the treatment of cardiovascular risk factors involves the use of antiplatelet medications or, when atrial fibrillation or valvular disease are involved, anticoagulation. In many cases, antithrombotics are indicated for the secondary prevention of ischemic stroke.

An exception that requires more careful consideration is when patients have CAA, given the increased risk of ICH (found to be approximately 5% annually in patients with CAA[97] with no prior ICH and approximately 10% annually for recurrent ICH[98]). Current guidance suggests that antiplatelet drugs can and should be safely used when clinically indicated for secondary prevention of cardiovascular and cerebrovascular events and also when indicated post–cardiac procedure (eg, coronary stent placement).[68] However, they should be avoided for primary prevention.[99]

The decision to anticoagulate in patients with CAA is more nuanced and requires careful risk-benefit discussions with patients and families. When required short term (eg, for cardiac thrombus or pulmonary embolism), the benefits likely outweigh the risks, but repeated evaluation to minimize the duration of anticoagulation use should be emphasized.[68] Long-term anticoagulation should be avoided in all patients with CAA, if possible, and novel anticoagulants are preferred if needed. New devices that allow for left atrial appendage closure in the setting of atrial fibrillation now exist and have been shown to be noninferior to warfarin and apixaban in preventing ischemic stroke.[100] In patients with valvular disease who have CAA, it may be worth discussing replacement with a bioprosthetic valve to avoid anticoagulation (which is required with mechanical valves).[68]

Notably, cerebral superficial siderosis has been found to be one of the greatest predictors of future ICH, and therefore patients with CAA with this finding should be approached even more cautiously when it comes to antithrombotic medications.[101]

Treatment

Unfortunately, except with regard to subacute recovery poststroke, vascular cognitive impairment and dementia is generally not reversible. Given its heterogeneity, little evidence exists for symptomatic management specifically for vascular cognitive impairment and dementia, but some of the options that have been evaluated are discussed below.

PHARMACOLOGIC TREATMENT.—Acetylcholinesterase inhibitors, which increase the availability of acetylcholine in the synaptic cleft and may also increase cerebral blood flow, are FDA approved for use in Alzheimer dementia but not specifically for vascular cognitive impairment and dementia. Confluent white matter hyperintensities (eg, as seen in subcortical ischemic vascular dementia and CADASIL) can disrupt cholinergic pathways.[102] Multiple trials have evaluated the efficacy of acetylcholinesterase inhibitors on vascular cognitive impairment and dementia, with inconsistent results. Several studies showed some improvement in cognition in patients with vascular cognitive impairment and dementia with the use of donepezil 5 mg/d[103] and 10 mg/d[104] and galantamine 8 mg to 12 mg 2 times a day.[105] In evidence-based reviews, donepezil is considered to be of modest cognitive benefit for vascular dementia, and galantamine may be of modest cognitive benefit for patients with mixed Alzheimer/vascular dementia (Class IIa, Level A recommendation).[4] The most common side effects of acetylcholinesterase inhibitors include diarrhea, nausea, and anorexia. They should be avoided in individuals with first-degree atrioventricular block.

Memantine is another FDA-approved medication for use in moderate to severe Alzheimer dementia and works as an *N*-methyl-D-aspartate (NMDA) receptor antagonist. Memantine 20 mg per day[106] or split 2 times a day[107] given to patients with vascular dementia was shown to result in an improvement across several cognitive scales but showed no improvement in global functioning. It is considered to be of modest cognitive benefit in vascular dementia (Class IIb, Level A recommendation).[4] The most common side effects for memantine include dizziness, constipation, and agitation.

Other medications (such as the calcium channel blockers nimodipine and nicardipine) and supplements (such as citicoline, vitamin B_{12}, and folic acid) have been evaluated in the treatment of vascular cognitive impairment and dementia.[72,108] Unfortunately, no consistent evidence of their benefits has been found, although evaluations are ongoing.

REHABILITATION.—The handful of studies that have been completed to date on vascular cognitive impairment and dementia due to subcortical ischemic vascular dementia indicate some efficacy of cognitive rehabilitation. The Cog-VACCINE (Cognitive Training in Patients With Vascular Cognitive Impairment, No Dementia) study showed improved global cognitive function after a 7-week computerized cognitive training course as well as increased functional connectivity between the left dorsolateral prefrontal cortex and medial prefrontal cortex after training.[109] The RehAtt (Rehabilitation of Attention in Patients With MCI and Brain Subcortical Vascular Changes Using the APT-II) study also showed improvements in working memory and attention as well as increased synchronization of activity in cerebellar areas on resting-state functional MRI (fMRI) with the use of a cognitive rehabilitation program.[110]

CONCLUSION

Vascular cognitive impairment and dementia is a heterogeneous entity that is nonetheless unique among the other causes of dementia in that, in most cases, its risk factors are readily identifiable and modifiable. Midlife control of vascular risk factors is the best step toward prevention of vascular cognitive impairment and dementia, and continued risk factor control

reduces the risk of progression in the disease. Unfortunately, treatment to improve cognition after the onset of vascular cognitive impairment and dementia has proven to be challenging, but further studies are ongoing to identify both pharmacologic and nonpharmacologic therapies for this purpose.

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KEY POINTS

- Vascular cognitive impairment and dementia refers to cognitive impairment or dementia that results from vascular brain injury. Vascular brain injury refers to damage to brain parenchyma resulting from ischemia, infarction, and hemorrhage.
- The most common risk factors for vascular cognitive impairment and dementia are cardiovascular risk factors, including hypertension, hyperlipidemia, type 2 diabetes mellitus, smoking, and atrial fibrillation.
- Vascular dementia is traditionally thought to be the second most common cause of dementia in the United States, comprising approximately 15% to 20% of clinically diagnosed dementia cases in North America and Europe.
- The probability of mixed dementia increases with increasing age, and the combination of multiple pathologies has been shown to be significantly correlated with the risk of clinical dementia.
- The pathogenesis of vascular cognitive impairment and dementia may be proposed as follows: vascular risk factors lead to cerebrovascular disease that results in vascular brain injury, and disruption of cognitive networks due to vascular brain injury leads to vascular cognitive impairment and dementia.
- Parkinsonism due to vascular brain injury may mimic idiopathic Parkinson disease, with bradykinesia, gait disturbance, and rigidity.
- The Montreal Cognitive Assessment has been shown to capture deficits due to vascular brain injury with greater sensitivity than the Mini-Mental State Examination given its more robust measures of executive dysfunction.
- The most common dementia mixed with vascular cognitive impairment and dementia is Alzheimer disease.
- White matter changes associated with cerebral amyloid angiopathy can be virtually indistinguishable from those caused by cardiovascular risk factors.
- The distinguishing clinical history with vascular cognitive impairment and dementia caused by cerebral amyloid angiopathy includes slowly progressive cognitive decline (as would be seen in Alzheimer dementia), episodic transient focal neurologic episodes (so-called amyloid spells), and sudden-onset focal neurologic deficits secondary to cortical lobar intracerebral hemorrhages.
- A strong family history of vascular cognitive impairment and dementia without significant cardiovascular risk factors may be suggestive of CADASIL/CARASIL, which is important to identify given its implications for future generations.

- Of the acquired dementias, vascular dementia is unique in that it has known modifiable risk factors and may, in fact, be nondegenerative if those risk factors are well controlled.
- In late life or in people with significant confluent white matter hyperintensities (Fazekas scale grade 3) due to arteriolosclerosis, it seems prudent to maintain systolic blood pressure in the 120 mm Hg to 140 mm Hg range.
- No strong evidence suggests that statins should be discontinued or avoided for concern of cognitive impairment, and rather, the known cardiovascular benefit of statin use argues in favor of continued statin use and low-density lipoprotein cholesterol reduction for secondary prevention.
- Cerebral superficial siderosis has been found to be one of the greatest predictors of future intracerebral hemorrhage in patients with cerebral amyloid angiopathy.
- Donepezil is considered to be of modest cognitive benefit for vascular dementia, and galantamine may be of modest cognitive benefit for patients with mixed Alzheimer/vascular dementia (Class IIa, Level A recommendation).

CASE 5–1

A 76-year-old man with a past medical history of hypertension and hyperlipidemia presented with a 2-year history of short-term memory decline. His family had noted changes in his personality as well, with decreased initiation. He was no longer engaged and interested in his family's affairs, including spending time with his grandchildren, which he previously enjoyed. He appeared to be generally apathetic. He could bathe and dress himself but required repeated reminders and encouragement from his family to do so. His responses and movements were slowed.

On mental status examination, he scored 19/30 on the Montreal Cognitive Assessment (MoCA), with noted attentional deficits (unable to do digits forward or backward) and poor memory (with 0/5 words recalled, which improved to 3/5 with category cues). On the remainder of his neurologic examination, he was noted to have slightly increased tone in bilateral upper extremities and slightly decreased right arm swing when walking. An MRI was obtained, which showed multiple lacunar infarcts involving the frontal-subcortical circuits bilaterally, with sparing of the hippocampi. (FIGURE 5-6).

COMMENT

This patient's MRI showed multiple lacunar infarcts bilaterally (FIGURE 5-6A). Of note, multiple infarcts can be seen in the bilateral striatum, resulting in disruption of the frontal-subcortical circuits and thus the patient's loss of motivated behavior, as well as disruption of motor pathways of the basal ganglia, resulting in vascular parkinsonism. His white matter disease is grade 2 on the Fazekas scale (described later in this article) (FIGURE 5-6B). Bilateral sparing of the hippocampi is seen (FIGURE 5-6C). On follow-up MRI 3 years later, with continued poor cardiovascular risk factor control, progression of white matter disease (FIGURES 5-6D and 5-6E) and unchanged relative sparing of bilateral hippocampi are seen (FIGURE 5-6F).

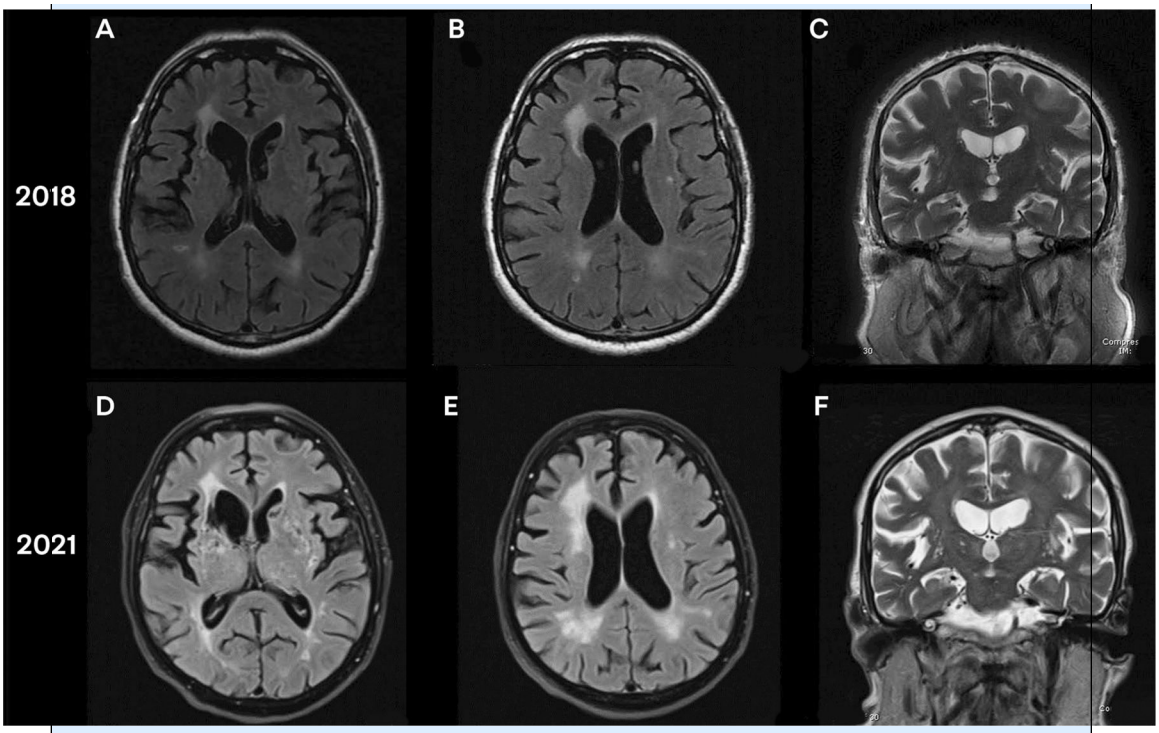

FIGURE 5–6.
Imaging of the patient in CASE 5-1. *A*, Axial fluid-attenuated inversion recovery (FLAIR) MRI shows lacunar infarct of bilateral caudate and right external capsule from initial presentation. *B*, Axial FLAIR MRI shows white matter disease (Fazekas scale grade 2) from initial presentation. *C*, Coronal T2-weighted MRI shows hippocampal sparing from initial presentation. *D*, Axial FLAIR MRI shows progression of white matter disease and lacunar infarcts on left basal ganglia as well as adjacent to right anterior horn, 3 years later. *E*, Axial FLAIR MRI shows white matter disease (Fazekas scale grade 3), 3 years later. *F*, Coronal T2-weighted MRI shows continued hippocampal sparing, despite progression in generalized atrophy (slight enlargement of ventricles can be seen), 3 years later.

CASE 5–2

A 79-year-old woman presented for evaluation of short-term memory loss. She had a past medical history of hypertension, diabetes, hyperlipidemia, and stroke. Her first stroke occurred in her left posterior cerebral artery territory 8 years before evaluation and resulted in right homonymous hemianopia; 1 year later, she had a cerebral infarction of the right periventricular centrum semiovale. Her memory had been impaired since then, and she was reliant on her family members for all instrumental and basic activities of daily living.

On neurologic examination, she was noted to have a dense right homonymous hemianopia, a left hemiparesis with increased tone, and hyperreflexia. On mental status examination, she scored 15/30 on the Mini-Mental State Examination (MMSE). Notably, her attention was preserved, with 3/3 on her registration trial for verbal memory; however, with delayed recall, she was unable to remember any of the three words.

Her clinical history was most consistent with poststroke dementia. An MRI was obtained, which showed her prior strokes as well as encephalomalacia involving the left hippocampus and mild atrophy of the right hippocampus (FIGURE 5-9).

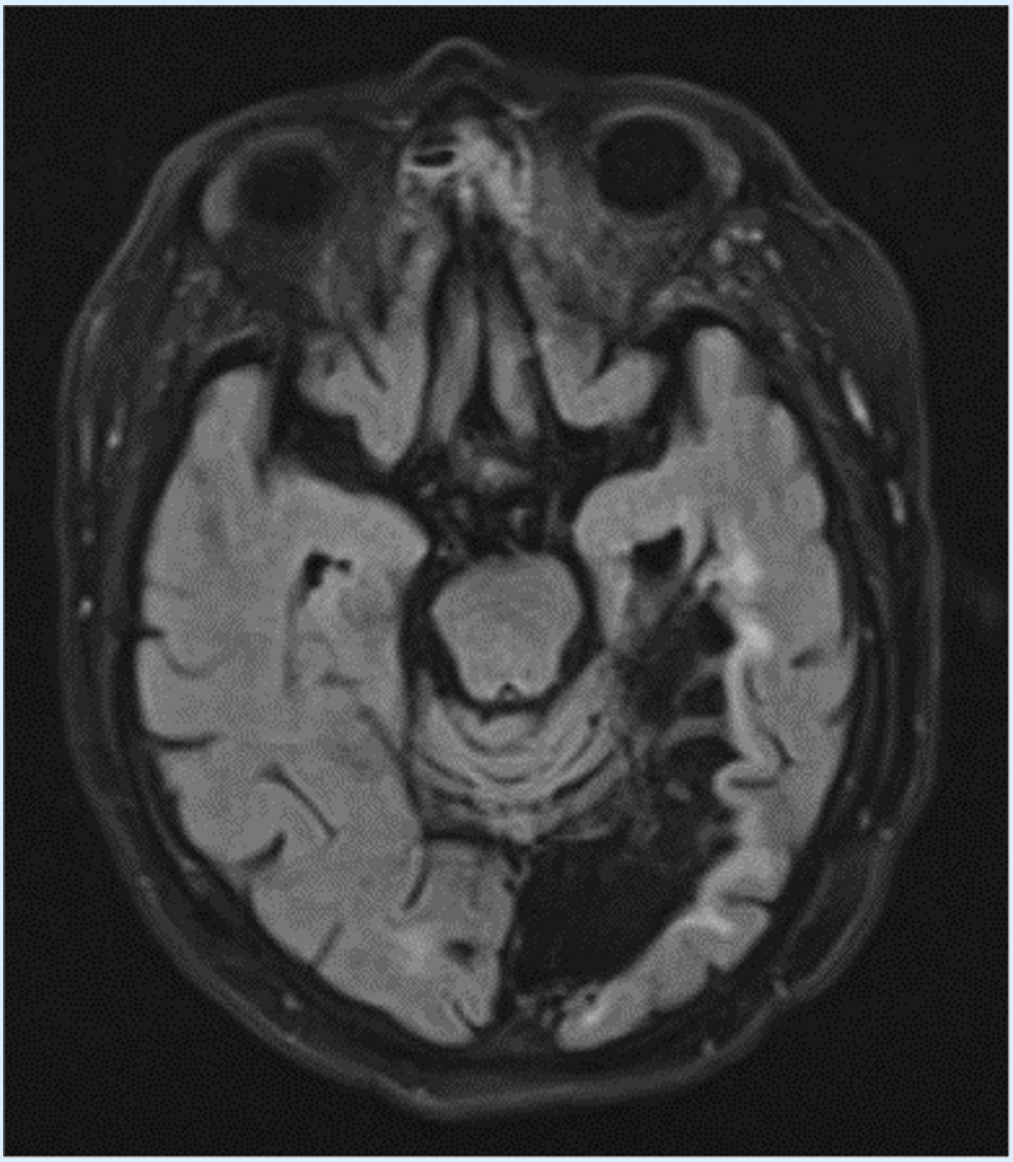

FIGURE 5–9.
Imaging of the patient in CASE 5-2. Axial fluid-attenuated inversion recovery (FLAIR) MRI shows encephalomalacia in the left posterior cerebral artery territory as well as hippocampal atrophy, left greater than right.

COMMENT

This patient had focal neurologic findings consistent with her known history of stroke in the left posterior cerebral artery territory and right centrum semiovale. The posterior cerebral artery also supplies blood flow to the hippocampus via the posterior choroidal artery, a branch off the P2 segment; consistent with this, her MRI showed encephalomalacia involving the left hippocampus. She was also found to have mild atrophy of the right hippocampus. The combination of these findings explains her stepwise decline and poor episodic memory.

CASE 5–3

An 86-year-old man with a history of polio, atrial fibrillation (on anticoagulation), hypertension, and hyperlipidemia had been followed for several years for memory decline, initially concerning for vascular cognitive impairment given his multiple cardiovascular risk factors. Over the course of several years, his pattern of cognitive decline revealed increasing amnestic impairment, concerning for mixed Alzheimer dementia and vascular cognitive impairment and dementia.

On neurologic examination, he scored 11/30 on the Montreal Cognitive Assessment (MoCA), with deficits in temporal orientation, and 0/5 on the delayed recall task, with no improvement with cueing. On executive function tasks, he had impairment on task switching and difficulty in accurate hand placement on clock drawing. The remainder of his neurologic examination was remarkable only for right leg weakness due to polio, for which he used a leg brace to ambulate.

An MRI was obtained, which showed significant superficial siderosis, particularly along the right parietal sulci (FIGURE 5-12A), and evidence of hemosiderin deposition in the left frontal lobe (FIGURE 5-12B). An amyloid positron emission tomography (PET) scan was obtained, which confirmed amyloid positivity, consistent with cerebral amyloid angiopathy (CAA) and Alzheimer disease (FIGURE 5-12C). Throughout his clinical course, he reported multiple episodes of transient left-sided symptoms, including left facial droop, left eye ptosis, left upper extremity weakness and numbness, and slurred speech, with each episode lasting less than 10 minutes. Workup for stroke/transient ischemic attack, seizure, and vascular insufficiency was unremarkable.

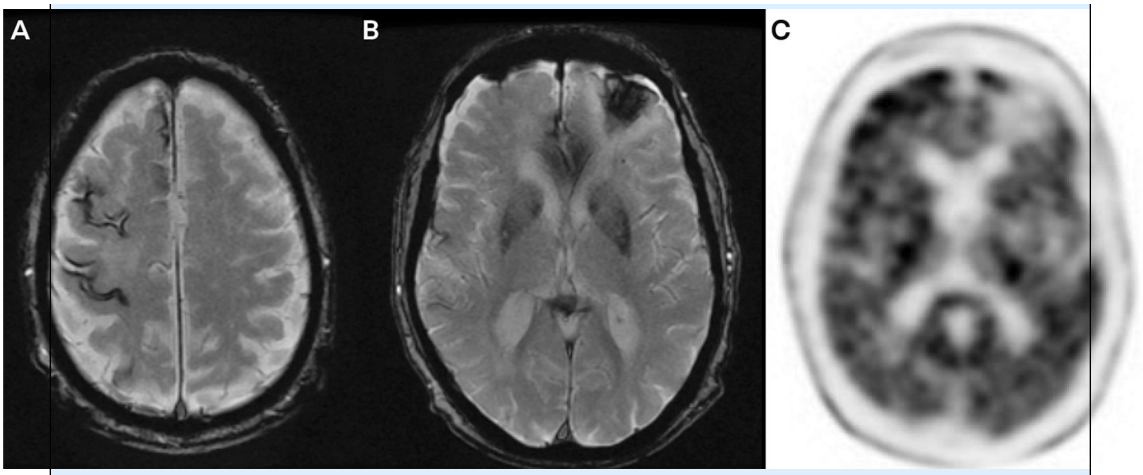

FIGURE 5–12.
Imaging of the patient in CASE 5-3. *A*, Axial gradient recalled echo (GRE) MRI shows superficial siderosis along the right parietal and right frontal sulci, consistent with cerebral amyloid angiopathy. *B*, Axial GRE MRI shows hemosiderin deposition in the left frontal lobe. *C*, Axial amyloid positron emission tomography (PET) shows amyloid positivity consistent with cerebral amyloid angiopathy and Alzheimer pathology.

COMMENT

This patient's episodic left-sided symptoms, in combination with MRI findings of superficial siderosis along the right parietal sulci, most likely reflected the amyloid spells of CAA rather than transient ischemic attacks. It is unclear whether the hemosiderin deposition in the left frontal lobe represented primary cortical intracerebral hemorrhage (commonly seen in CAA) or left frontal embolic infarct with hemorrhagic conversion (given his history of atrial fibrillation). Superficial siderosis is a significant risk factor for intracerebral hemorrhage, thus consideration of left atrial appendage closure in lieu of chronic anticoagulation for atrial fibrillation is indicated in this case.

CASE 5–4

A 73-year-old woman presented to the behavioral neurology clinic with a 1-year history of cognitive decline. The patient's husband described that she first started having difficulty following the plots of her favorite television shows and more recently had been confused about where she was at times. She had a 6-year history of intermittent, difficult-to-control, generalized tonic-clonic seizures that had resulted in multiple hospitalizations. She had no significant cardiovascular risk factors. She denied a history of headaches, and her cognition at the time of seizure onset was unchanged from her prior baseline. Her family history was positive for her mother having seizures and dementia, ultimately passing away in her early eighties.

Her Mini-Mental State Examination (MMSE) score was 6/30, with significant impairment in executive function, recent memory, language, and processing speed. Her neurologic examination was unremarkable, except for a slightly wide-based gait. Brain MRI showed confluent white matter disease (FIGURE 5-13A), with striking involvement of the white matter of the temporal poles (left more than right) (FIGURE 5-13B). Diffuse and numerous microbleeds were seen throughout the temporal lobes bilaterally (FIGURE 5-13C), Genetic testing confirmed an atypical heterozygous pathogenic variant in *NOTCH3* (c.1759C>T).

COMMENT

This patient's MRI findings lend a clue to the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) given the confluent white matter disease with involvement of the temporal poles, which is not often seen in vascular brain injury due to cardiovascular risk factors. Although CADASIL is usually associated with the classic symptoms of migraine and strokes, a subset of atypical variants can present with seizures and a subcortical pattern of cognitive impairment, and imaging may show microbleeds in both deep and peripheral locations. These patients tend to present at an older age than patients with classic CADASIL.

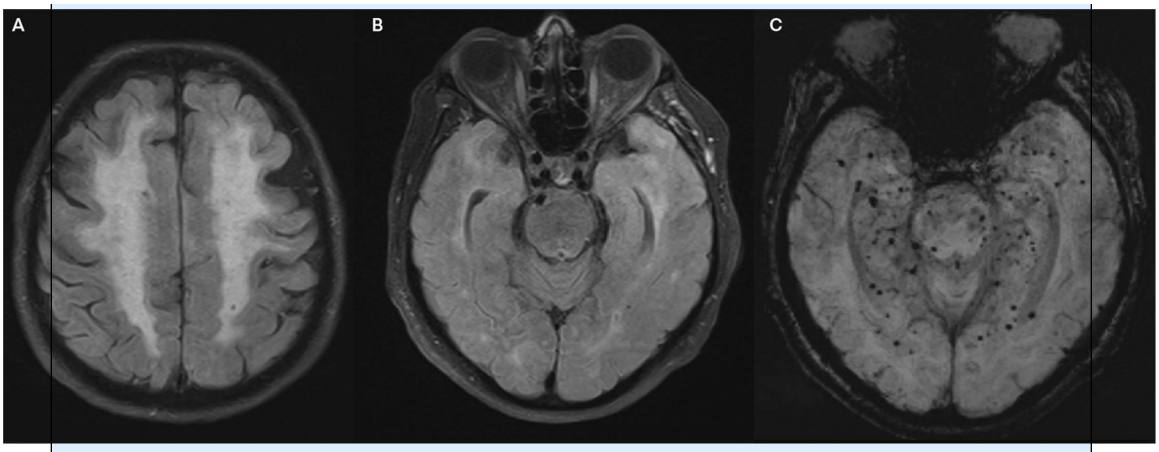

FIGURE 5–13.
Imaging of the patient in CASE 5-4. *A*, Axial fluid-attenuated inversion recovery (FLAIR) MRI shows severe confluent white matter disease consistent with Fazekas scale grade 3. *B*, Axial FLAIR MRI slice through the temporal lobes shows confluent white matter disease involving the temporal poles, left more than right. *C*, Axial gradient recalled echo (GRE) MRI shows innumerable microbleeds throughout the temporal lobes bilaterally.

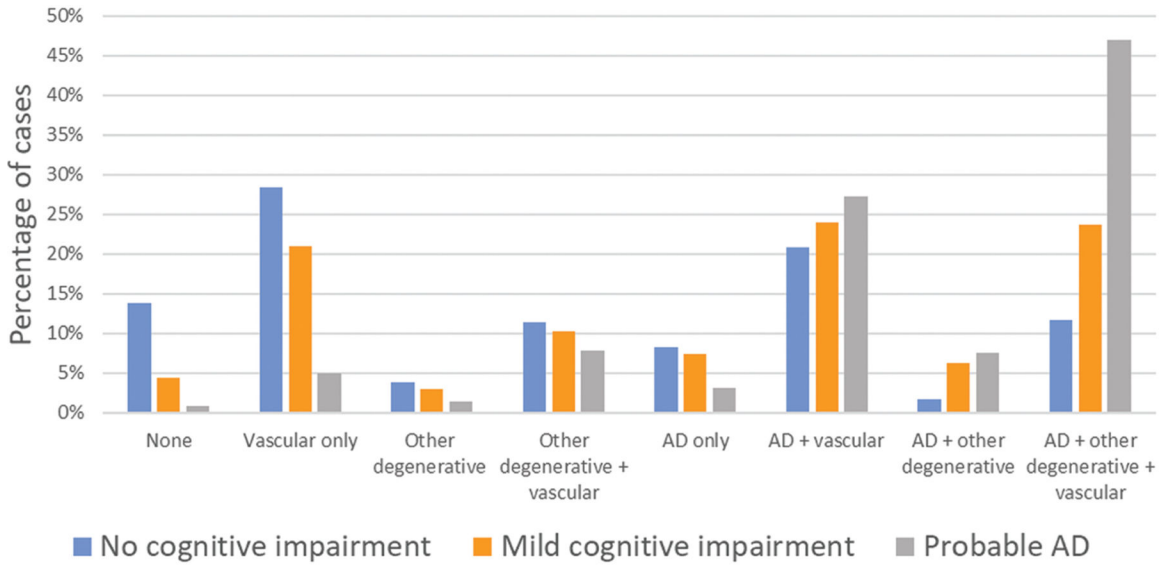

FIGURE 5–1.

Prevalence of different neuropathologies among the participants in the Rush Religious Orders Study/Memory and Aging Project (ROS/MAP) who clinically had no cognitive impairment, mild cognitive impairment, or probable Alzheimer disease (AD) (n = 1078). "Other degenerative" refers to other neurodegenerative pathology, including Lewy body, transactive response DNA-binding protein 43 (TDP-43) and hippocampal sclerosis. Notably, when compiled, mixed pathology increases from about 46% of participants with no cognitive impairment to 89.7% of participants with probable AD.

[a] Data from Kapasi A, et al, Acta Neuropathologica.[14]

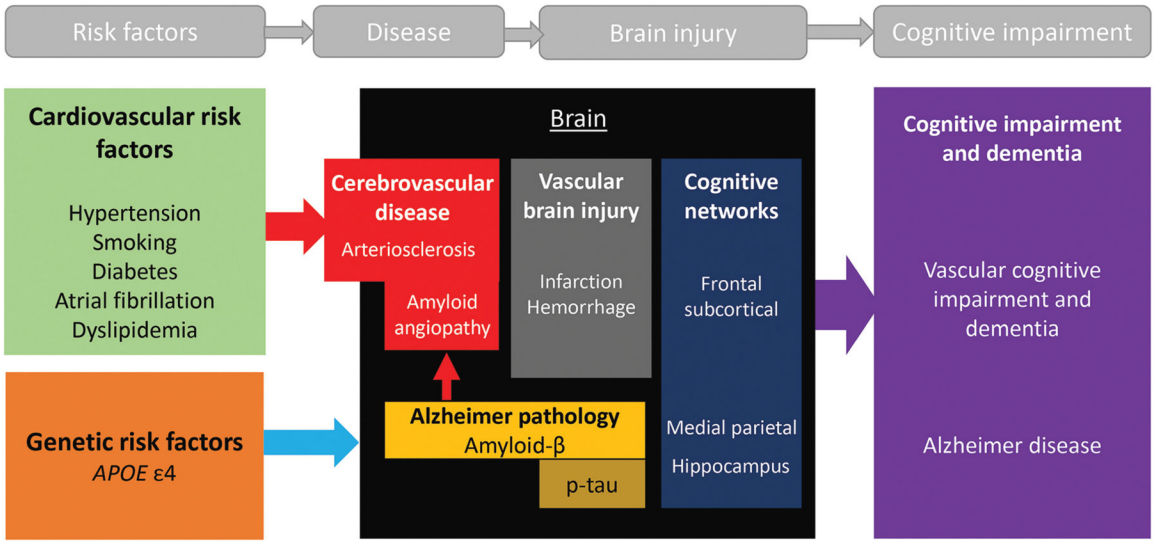

FIGURE 5–2.

Pathogenesis of vascular cognitive impairment and dementia and mixed Alzheimer disease/vascular cognitive impairment and dementia. Cardiovascular risk factors are the leading cause of atherosclerotic cardiovascular disease (ASCVD), which results in cerebral vascular disease and, uncontrolled, may result in vascular brain injury and ultimately vascular cognitive impairment and dementia. Apolipoprotein E4 (*APOE* ε4) is associated with Alzheimer disease (AD) and cerebral amyloid angiopathy (CAA) and is a frequent cause of mixed AD/vascular cognitive impairment and dementia. Vascular brain injury can result in damage to the frontal subcortical circuits, whereas AD tends to affect the medial parietal and hippocampal regions.

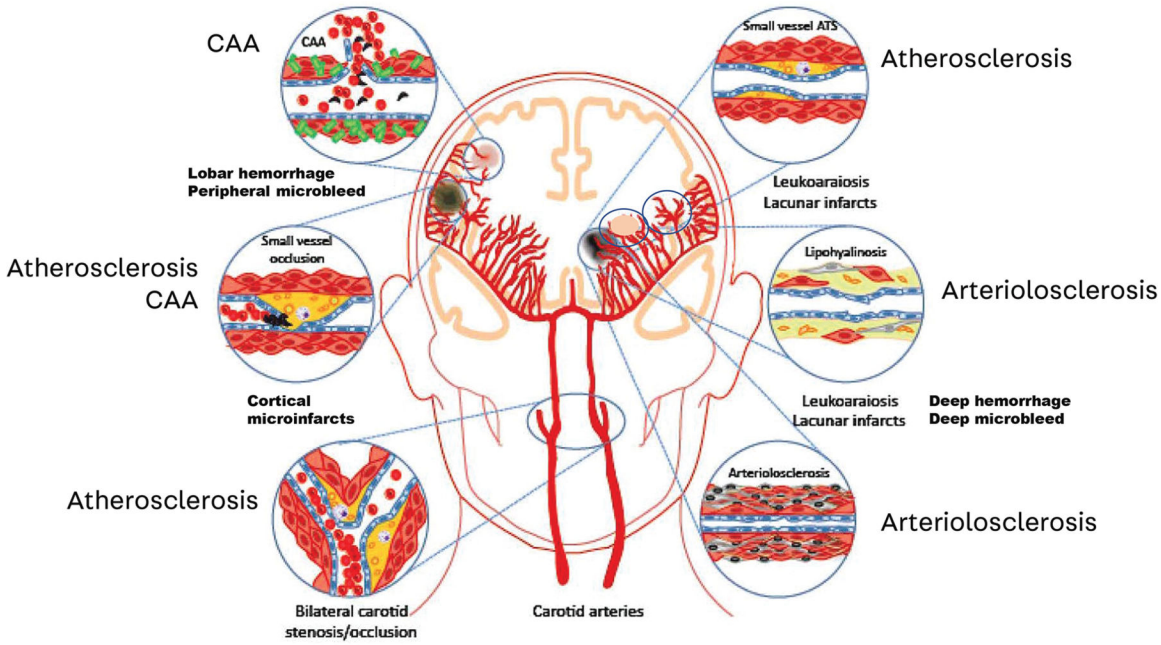

FIGURE 5–3.

The different forms of cerebral vascular disease that may contribute to vascular cognitive impairment and dementia.

ATS = atherosclerosis; CAA = cerebral amyloid angiopathy.

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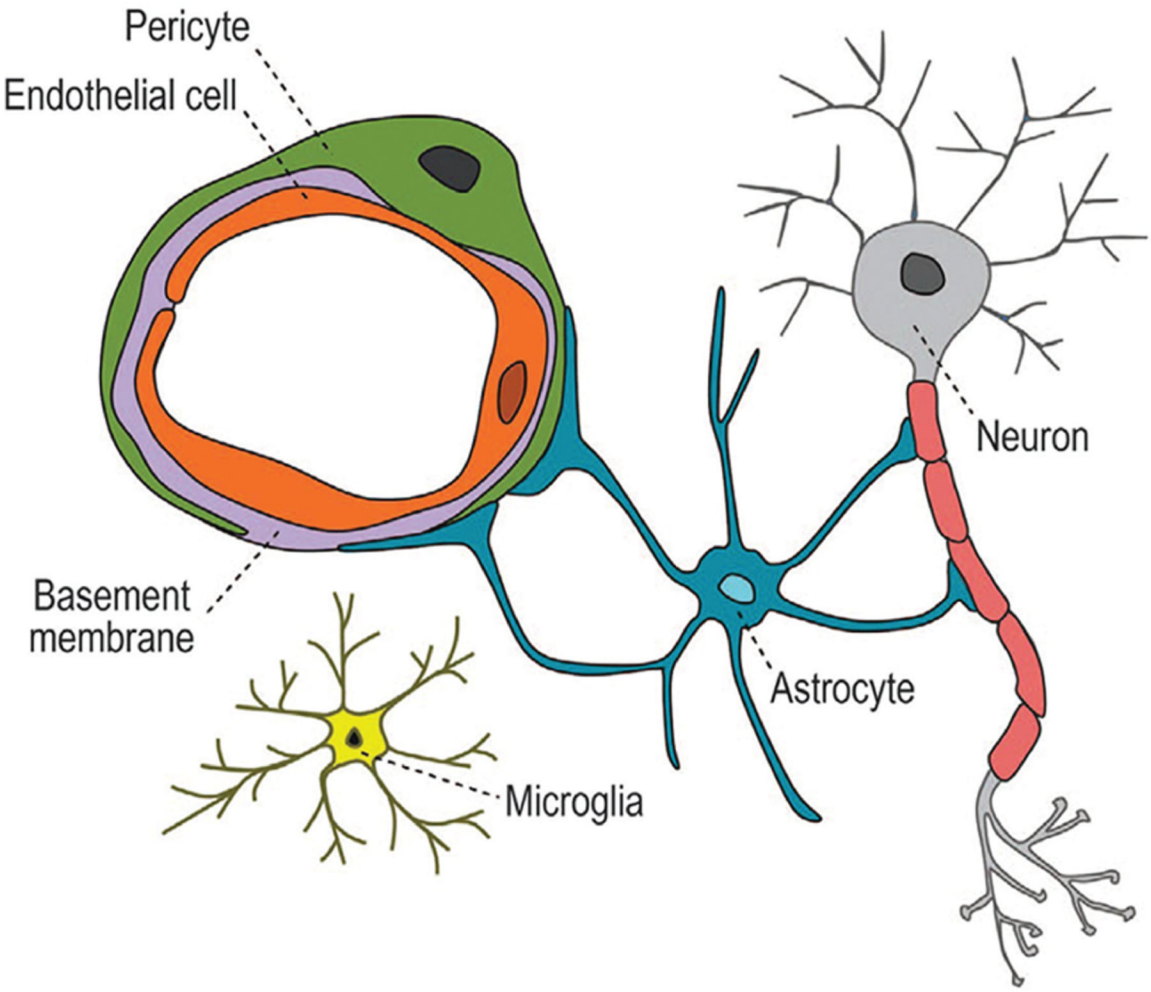

FIGURE 5–4.
The parts of the neurovascular unit.
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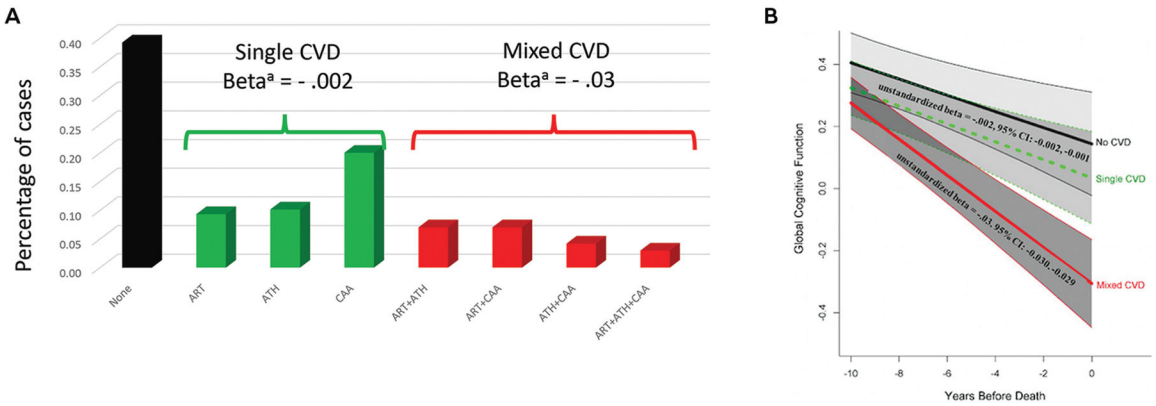

FIGURE 5–5.

The association of single (*green*) and mixed (*red*) cerebrovascular disease (CVD) profile groups with global cognitive decline compared with participants with no cerebrovascular disease (*black*). In an autopsy series on participants with Alzheimer disease from the Rush Religious Orders Study, Rush Memory and Aging Project, and the Minority Aging Research Study, the major types of cerebrovascular disease (CVD) and their various combinations were examined. Notably, mixed CVD produced greater cognitive decline over time when compared to single or no CVD groups.

[a] Unstandardized beta for rate of cognitive decline for single CVD and mixed CVD compared to reference group with no CVD.

ART = arteriolosclerosis; ATH = atherosclerosis; CAA = cerebral amyloid angiopathy.

Panel B reprinted with permission from Lamar M, et al.[35] © 2021 American Heart Association, Inc.

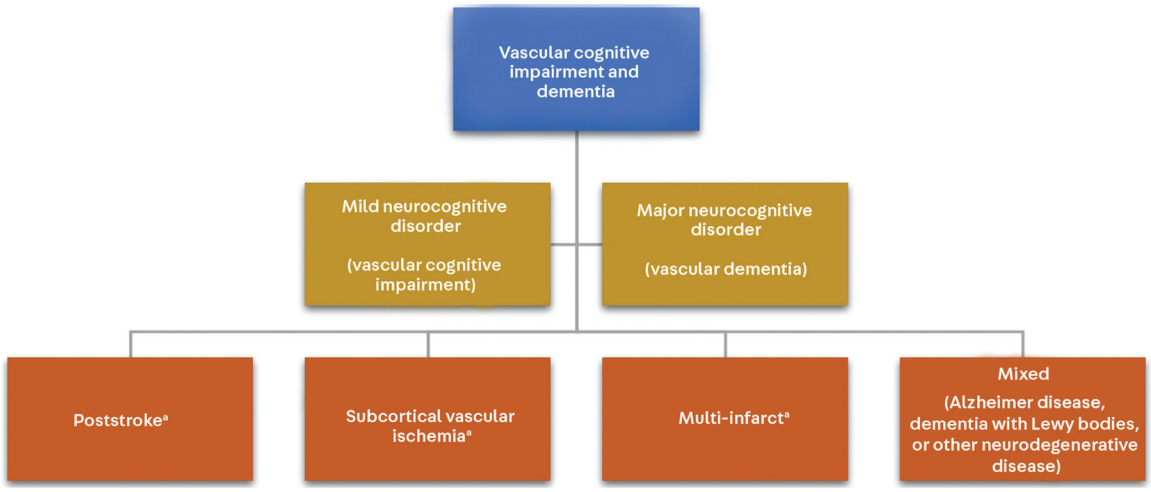

FIGURE 5–7.
The VICCCS (Vascular Impairment of Cognition Classification Consensus Study) criteria for vascular cognitive impairment and dementia.
[a] Although these subtypes are listed separately from "mixed," any subtype of vascular cognitive impairment and dementia has the potential to have mixed pathology.
Modified with permission from Skrobot O, et al, Alzheimers Dement.[41] © 2016 The Alzheimer's Association.

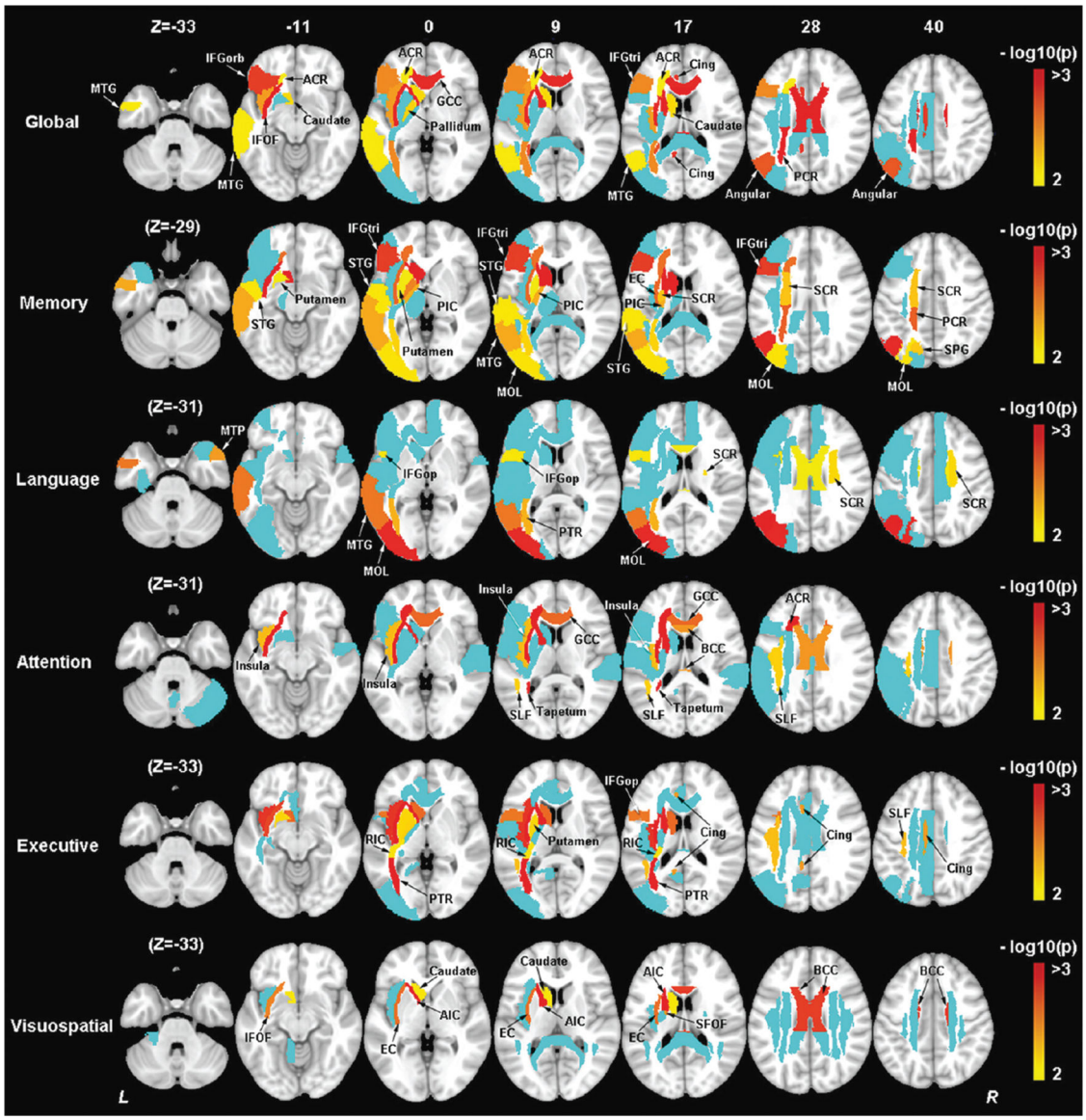

FIGURE 5–8.

How infarct location is linked to cognitive function. The *yellow* to *red* coloration shows the level of statistical association between infarcts in those locations and cognitive function in multivariate region of interest-based analyses. *Light blue* corresponds to areas associated with cognition in univariate analyses.

ACR = anterior corona radiata; AIC = anterior limb of internal capsule; BCC = body of corpus callosum; Cing = cingulum (white matter); EC = external capsule; GCC = genu of corpus callosum; IFGop = inferior frontal gyrus (opercular); IFGorb = inferior frontal gyrus (orbital); IFGtri = inferior frontal gyrus (triangular); IFOF = inferior fronto-occipital fasciculus; MOL = middle occipital lobe; MTG = middle temporal gyrus; MTP = middle temporal pole; PCR = posterior corona radiata; PIC = posterior limb of internal capsule; PTR = posterior thalamic radiation; RIC = retrolenticular part of internal capsule; SCR

= superior corona radiata; SFOF = superior fronto-occipital fasciculus; SLF = superior longitudinal fasciculus; SPG = superior parietal gyrus; STG = superior temporal gyrus. Reprinted with permission from Zhao L, et al, J Cereb Blood Flow Metab.[45] © 2018 SAGE Publications.

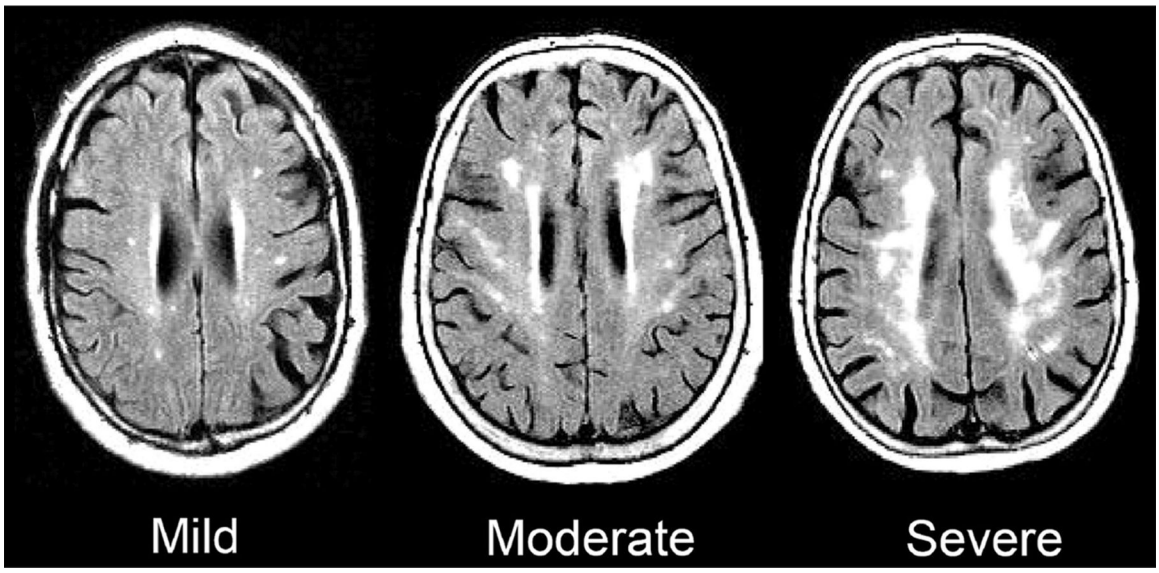

FIGURE 5–10.
Visual reference for the Fazekas scale.
Reprinted with permission from Inzitari D, et al, BMJ.[48] © 2009 BMJ Publishing Group Ltd.

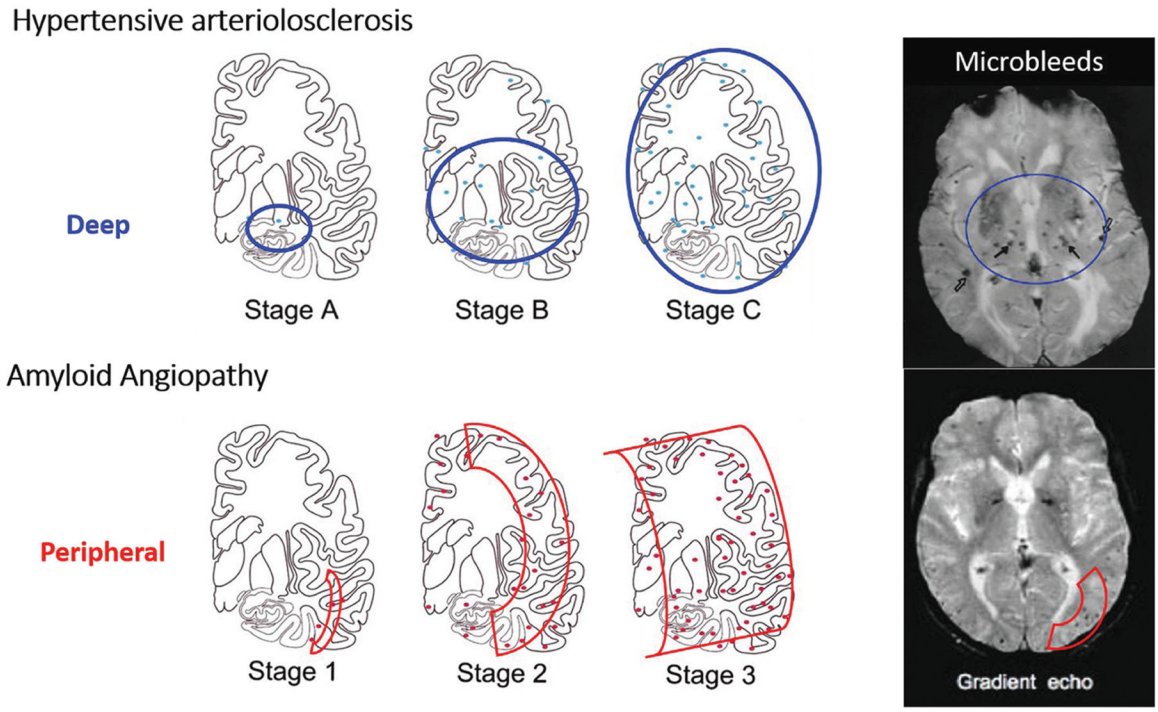

FIGURE 5–11.

Distinguishing the location and staging the severity of microbleeds. Hypertensive arteriosclerosis generally results in deep microbleeds, indicated by *blue ovals*, whereas amyloid angiopathy is characterized by peripheral microbleeds, indicated by *red shapes*. Modified with permission from Thal DR, et al, J Neuropathol Exp Neurol.[51] © 2003 Oxford University Press.

TABLE 5–1

Clinical Comparison of Vascular Cognitive Impairment and Dementia and Alzheimer Disease

Evaluation	Vascular cognitive impairment and dementia	Alzheimer disease
History		
History of present illness	Multi-infarct/poststroke: stepwise (temporal relationship) Subcortical ischemic vascular disease: slowly progressive	Slowly progressive
Past medical/family history	Cerebrovascular disease, coronary artery disease, peripheral vascular disease	Alzheimer disease
Mental status	Multi-infarct/poststroke: location-dependent Subcortical ischemic vascular disease: dysexecutive function	Amnestic-type memory impairment (poor cueing, rapid forgetting)
Physical examination		
Neurologic	Focal signs, gait disturbance	Normal neurologic examination other than mental status (until later stages)
Cardiovascular	Changes consistent with cardiovascular risk factors (retinal, carotid, peripheral artery disease), high blood pressure	Normal
Laboratory tests	Elevated hemoglobin A_{1c}, lipids; check ECG for atrial fibrillation Routine laboratory tests for reversible dementia (comprehensive metabolic panel, complete blood cell count, thyroid-stimulating hormone [TSH], vitamin B_{12} level, fluorescent treponemal antibody absorption) should be negative	Routine laboratory tests for reversible dementia (comprehensive metabolic panel, complete blood cell count, thyroid-stimulating hormone [TSH], vitamin B_{12} level, fluorescent treponemal antibody absorption) should be negative
Structural imaging		
MRI/CT	Focal infarcts in strategic location, confluent white matter changes, generalized atrophy	Hippocampal, temporal, parietal, and frontal atrophy
Metabolic imaging		
FDG-PET	Multifocal hypometabolism depending on areas of vascular brain injury	Hypometabolism in parietal, temporal, and frontal lobes with sparing of primary motor-sensory cortex
Biomarkers	None	CSF or PET amyloid-β or phosphorylated tau

CSF = cerebrospinal fluid; CT = computed tomography; ECG = electrocardiogram; FDG-PET = fludeoxyglucose positron emission tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

TABLE 5–2

Grading for the Fazekas Scale[a]

Grade	Periventricular white matter	Deep white matter
0 = Normal	Absent	Absent
1 = Mild	Caps or pencil-thin lining	Punctate foci
2= Moderate	Smooth halo	Beginning confluence
3 = Severe	Irregular periventricular signal extending into the deep white matter	Large confluent areas

[a]Modified from Kim W, Yang DW.[49] © 2012 Korean Dementia Association.

TABLE 5–3

Genes Associated With Inherited Small Vessel Disease[a]

Gene	Chromosomal location	Known function of gene product	Associated subtype of small vessel disease
Mendelian/monogenic			
NOTCH3[b]	*19p13*	Transcription regulator in vascular smooth muscle cells	White matter hyperintensities, ischemic stroke, intracerebral hemorrhage (ICH) seen via radiography, CADASIL
COL4A1/A2[b]	*13q34*	Collagen IV, endothelial basement membrane protein	White matter hyperintensities, ischemic stroke, ICH
HTRA1[b]	*10q26*	Serine protease involved in repression of transforming growth factor β (TGF-β)	White matter hyperintensities, ischemic stroke, CARASIL
TREX1	*3p21*	3'-exonuclease involved in DNA repair	White matter hyperintensities, ischemic stroke
Contributory/polygenic			
FOXC1/FXF2	*6p25*	DNA regulation in eye, brain, heart, and kidney development	White matter hyperintensities, ischemic stroke
ZCCHC14	*16q24*	Transcription factor and metal ionbinding protein	White matter hyperintensities, stroke
WDR12/ICA1L	*2q33*	Protein domain-specific binding	White matter hyperintensities, stroke
PMF	*1q22*	Transcription factor involved in mitosis	White matter hyperintensities, ICH
APOE	*19q13*	Apolipoprotein involved in lipid transport and metabolism	Brain arteriolosclerosis, white matter hyperintensities, ischemic stroke
ABCC9	*12p12*	K+ channel regulator in blood vessels	Brain arteriolosclerosis in individuals >80 years old at death
JAZF1	*7p15*	Transcription factor involved in transcription repression	Brain arteriolosclerosis
TSPAN8	*12q21*	Cell-membrane protein involved in cell growth regulation	Brain arteriolosclerosis
LGR5	*12q21*	Receptor in Wnt signaling pathway	Brain arteriolosclerosis
KCNJ11	*11p15*	K+ channel regulated by ABCC8 and ABCC9	Brain arteriolosclerosis
PCSK9	*1p32*	Protease involved in cholesterol metabolism regulation	Brain arteriolosclerosis
ZFHX3	*16q22*	Transcription factor associatedwith atrial fibrillation	Brain arteriolosclerosis

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL = cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; DNA = deoxyribonucleic acid.

[a]Modified with permission from Blevins BL, et al, Acta Neuropathol.[69]

[b]For *NOTCH3*, *COL4A1/A2*, and *HTRA1*, gene variants also may be contributory in polygenic disease.

TABLE 5–4

The American Heart Association/American Stroke Association Guidelines for Optimal Brain Health[a]

Factor	Ideal definition
Hypertension	Untreated blood pressure <120/80 mm Hg (avoid hypotension)
Fasting blood glucose	<100 mg/dL (avoid hypoglycemia)
Total cholesterol	<200 mg/dL
Smoking status	Nonsmoker
Physical activity	Moderate-intensity activity >150 min/wk or vigorous intensity activity >75 min/wk or combination
Body mass index	<25 kg/m^2
Diet	Fruits and vegetables ≥4.5 cups/d
	Fish ≥ two 3.5-oz servings/wk (preferably oily fish)
	Fiber-rich whole grains (≥1.1 g fiber per 10 g of carbohydrate) three or more 1-oz equivalent servings/d
	Sodium <1500 mg/d
	Sugar-sweetened beverages ≤450 kcal (36-oz)/wk

[a]Modified with permission from Goshgarian C, Gorelick PB, Trends Cardiovasc Med.[75] © 2018 Elsevier Inc.