Understanding and Treating Vascular Cognitive Impairment

Philip B. Gorelick, MD, MPH, FAAN; David Nyenhuis, PhD, ABPP

ABSTRACT

Purpose of Review: It is estimated that one in three people will experience a stroke, dementia, or both during their lifetime. The goal of this article is to assist clinicians in the identification and treatment of patients with vascular cognitive impairment (VCI). To that end, we will discuss the scope and definition of VCI; how this definition can be applied in clinical practice; VCI epidemiology and pathogenesis, its clinical features, and assessment; and prevention and treatment of this disorder.

Recent Findings: During the past decade, we have gained a more complete understanding of clinical manifestations of VCI (eg, the importance of executive function and memory), what it looks like pathologically (eg, the role of cerebral amyloid angiopathy, microinfarcts, and ''silent'' strokes), and how VCI relates to other disease processes (eg, co-occurrence with Alzheimer disease). A recent American Heart Association and American Stroke Association guidance statement clarified the construct of VCI, including the severity of cognitive and behavioral dysfunction contained under the definition of VCI and the presence of both ''pure'' and ''mixed'' VCI forms. VCI treatments approved by the US Food and Drug Administration are still lacking, and challenges remain regarding how to convert promising observational study findings that link stroke and coronary heart disease risk factors to cognitive impairment and dementia into evidence-based preventive methods.

Summary: VCI is a common contributor to cognitive impairment in later life. Because the risk of Alzheimer disease may be heightened by the same risk factors that make us susceptible to stroke and coronary heart disease, these borderlands merit careful consideration as we strive to preserve cognitive function throughout the aging process.

Continuum (Minneap Minn) 2013;19(2):425–437.

DEFINITION AND SCOPE OF VASCULAR COGNITIVE IMPAIRMENT

The construct of cognitive impairment and dementia associated with cerebrovascular disease and stroke has gone through many permutations, from multi-infarct dementia to vascular dementia (VaD) to the presently used term, vascular cognitive impairment (VCI).[1] In a recent statement of the American Heart Association and American Stroke Association (AHA-ASA), VCI is defined as ''a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain.''[1] VCI therefore encompasses all of the potential levels of cognitive severity, from its mildest form detectable by neuropsychological assessment to full-blown VaD. VCI also includes both ''pure'' (cerebrovascular disease alone) and ''mixed'' (cerebrovascular disease with other

pathology, such as that of Alzheimer disease [AD]) pathologic conditions.

The National Institute of Neurological Disorders and Stroke and *Association Internationale pour la Recherché et l'Enseignement en Neurosciences* (NINDS-AIREN) criteria[2] are currently most widely used in VaD clinical trials. These criteria require neuroimaging evidence of focal brain damage, focal clinical signs, and cognitive deficits in at least three cognitive domains, one of which must be memory. The cognitive deficits must be linked to functional impairment. The strength of association between cerebrovascular disease and cognitive impairment is the primary determinant of probable versus possible VaD diagnoses. In clinicopathologic study, the NINDS-AIREN criteria have shown high specificity but low sensitivity, meaning that many true cases of VaD were not detected by the criteria. The recent AHA-ASA VCI statement includes updated diagnostic criteria for VCI. The guidelines include both VaD and vascular mild cognitive impairment (VaMCI) criteria, require fewer impaired cognitive domains than NINDS-AIREN criteria, and do not require memory impairment. They also introduce the term *unstable VaMCI* for use in patients who shift from an impaired to an unimpaired cognitive state—for example, if the patient demonstrates cognitive recovery from a vascular event. The AHA-ASA criteria have not yet been the subject of clinicopathologic study, so their sensitivity and specificity are not yet known.

EPIDEMIOLOGY
Incidence, Prevalence, and Mortality

It is estimated that one in three people will experience a stroke, dementia, or both. Strokes and AD often occur concomitantly and pose risks for one another.[3] Interestingly, ''silent'' strokes outnumber clinically manifest ones by a factor greater than 11 to 1 and are not so silent, as they are harbingers of future stroke and cognitive impairment. In addition, about one in 10 adults in the community harbor a silent stroke by an average age of approximately 63 years.[4]

Traditionally, after AD, VaD has been considered the second leading cause of progressive and irreversible dementia; however, currently Lewy body dementia is considered the second leading cause by some experts. Epidemiologic studies suggest that the incidence of dementia in Europe is highest for AD (60% to 70% of all cases), with VaD accounting for about 15% to 20% of cases.[5] In addition, incidence rates of these disorders increase with age but show geographical variation, such as being higher in northwestern than southern European countries,[5] and there may not be gender differences in the rates of risk for VaD as once thought.[6] Furthermore, considerable evidence indicates that stroke increases the risk of dementia,[7] and in some studies dementia after stroke has been reported in almost one-third of post-stroke patients within 3 months' time. The results of some epidemiologic studies in Asian countries suggest that, because of high stroke rates in the region, VCI may be more common there than AD.[8,9] The discordancy in rates among epidemiologic studies may in part reflect differences in classification systems used for dementia or cognitive impairment, other issues of disparate study methodologies, and the influence of improved stroke-prevention efforts.

Other groups that have been shown to be at risk for VCI include African Americans, patients with AD who have strokes, and the very elderly (who are also at risk of AD).[10] Neuropathologic studies show an additive influence or correlation between AD pathology and

cerebral infarction in the manifestation of cognitive impairment.[11] Furthermore, mixed neuropathology (ie, AD plus VCI changes) is common in people with dementia or AD.[12]

Cognitive impairment is associated with decreased survival. People with advanced dementia are subject to medical complications such as pneumonia, febrile episodes, and eating problems associated with eventual death when there is cognitively impairing disease.[13] Older people who survive severe sepsis are at risk of substantial and persistent new cognitive impairment and functional disability that may decrease their ability to live independently.[14] Traditionally, survival in AD is longer than in VaD or mixed dementia, but survival varies according to the patient's age, race or ethnic group, and severity of cognitive impairment. In a hospital-based study of African Americans with AD, VaD, or stroke without dementia who were followed for up to 7 years, there were no substantial differences in survival between any of the diagnostic groups after adjusting for age.[15]

Risk Markers and Factors

In the context of this review, *risk marker* refers to an exposure that increases the risk of a disease state or disorder, and *risk factor* refers to an exposure that not only increases the risk of the disease state or disorder but also has such a direct impact that the target disease or disorder is reduced when this factor is treated or modified. In some examples, the term "risk factor" is used interchangeably with "risk marker" for sake of simplicity and consistency in the literature. It has long been held that risks for stroke are also risks for VCI.[16] In a case-control study among 61 patients with multi-infarct dementia and 86 patients with stroke without cognitive impairment, stroke with dementia was predicted by ad-

vanced age, lower educational attainment, history of myocardial infarction, and recent cigarette smoking, whereas higher systolic blood pressure was associated with not having dementia.[16] The findings were among the earliest to suggest that risk factors for stroke and coronary heart disease (CHD) were risks for VCI as well. The relationship between blood pressure and risk of cognitive impairment is a complex one, discussed in greater detail in the section below on prevention and treatment of VCI. Conventional knowledge suggests that lowering blood pressure in patients who do not have cognitive impairment can reduce the risk of subsequent cognitive impairment, whereas lowering blood pressure to preserve cognition among patients who already have cognitive impairment remains unproven as a successful strategy.

In a subsequent companion study in which an AD comparison group was included, it was found that African Americans with a clinical diagnosis of AD frequently had risks for stroke (eg, 50% had hypertension, 15% CHD, and 13% diabetes mellitus).[17] When brain necropsy was performed in a subgroup of these patients who had a clinical diagnosis of AD and stroke or cardiovascular risk factors, there was good agreement between the neuropathologic diagnosis and the clinical diagnosis of AD.[18] The findings provided some of the early evidence to suggest that modifiable cardiovascular risks tend to be present in people with AD (**Case 8-1**).

Indeed, strokes and AD often occur concomitantly and pose risks for one another.[3] Risks for stroke, such as hypertension, hypercholesterolemia, hyperhomocysteinemia, elevated body mass index and fat intake, atrial fibrillation, diabetes mellitus, cigarette smoking, and metabolic syndrome, are now considered risks not only for VCI but
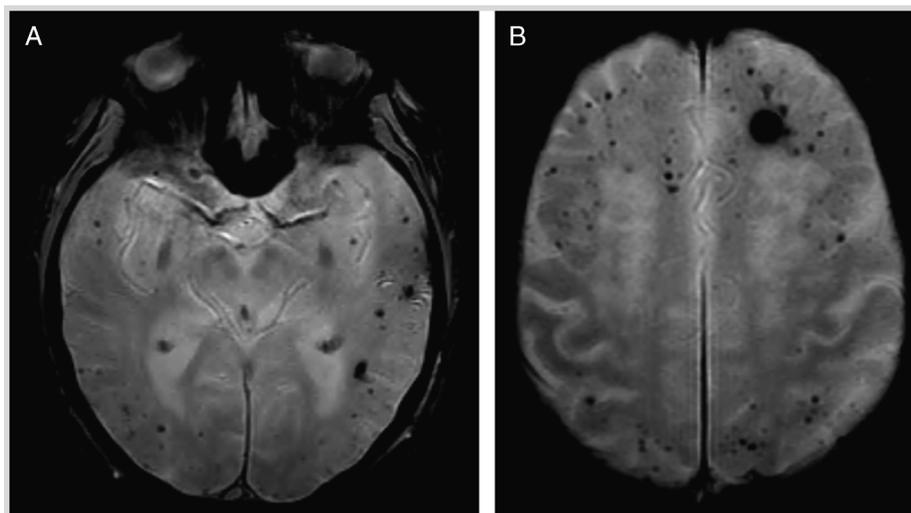
Case 8-1

A 79-year-old man presented with slight anomia, difficulty with recall at 5 minutes, and slightly unsteady gait. He scored 25/30 on the Mini-Mental State Examination. Instrumental and routine activities of daily living were not impaired. His medications included ramipril for high blood pressure and pioglitazone for diabetes (glycosylated hemoglobin was 7.0%). Blood pressure was 163/93 mm Hg. Other results of his general physical examination were unremarkable. MRI brain study (**Figure 8**-1) showed cerebral microbleeds on gradient-echo sequences, periventricular white matter disease predominantly in the subfrontal regions, and several scattered basal ganglia small vessel infarcts (not pictured).

Comment. The subfrontal white matter disease and cerebral microbleeds are manifestations of cerebral small vessel disease (cerebral amyloid angiopathy underlying the cerebral microbleeds, and deep penetrating vessel occlusive cerebral vascular disease underlying the lacunar infarcts and periventricular subfrontal white matter disease). Given the presence of cerebrovascular disease, mild cognitive deficits, and intact activities of daily living, the diagnosis was classified as vascular mild cognitive impairment. Formal neuropsychological testing supported the diagnosis with predominant executive dysfunction. The presence of cerebral microbleeds, however, raised concern about underlying Alzheimer disease and, therefore, a mixed vascular cognitive impairment and Alzheimer disease mechanistic process.[19]

FIGURE 8-1 Cerebral microbleeds. Gradient-echo MRI brain study showing multiple cortical cerebral microbleeds (*small, dark, circular areas in both hemispheres*) (*A*) with remnant of macrobleed in frontal area (*larger, frontal, dark, circular area*) (*B*).

Figure courtesy of Chelsea Kidwell, MD, Georgetown University, Washington, DC.

The addition of a diuretic gently lowered the patient's blood pressure to reach a systolic blood pressure of approximately 150 mm Hg, with no immediate complications.

While lowering blood pressure is not a well-established strategy for prevention of cognitive impairment or its progression, it does reduce stroke risk. The presence of silent strokes on brain MRI is a risk for clinically manifest stroke and cognitive impairment. The administration of antiplatelet therapy in the presence of cerebral microbleeds is controversial.[19] Cerebral microbleeds can be harbingers of cerebral macrobleeds, and some studies have suggested that when cerebral microbleeds are abundant, antithrombotic therapy elevates the risk of macrohemorrhage of the brain (this has not been definitively proven but remains a potential concern). After a patient-focused discussion, it was decided not to administer antiplatelet therapy. A glycosylated hemoglobin target of approximately 7.0% is reasonable, according to stroke prevention guidelines.

also for AD.[20] Cardiovascular factors have now been linked to AD as well as to cardiovascular disease and atherosclerosis. The recently published AHA-ASA guidance statement includes a list of key risk markers that may be linked to

VCI (**Table 8-1**).[1] Most of these factors are typical or usual cardiovascular risks or concomitant disorders or diseases. Factors labeled as uncertain in **Table 8-1** have relatively less epidemiologic supporting evidence of association with VCI. All of the factors (including those labeled as uncertain with respect to VCI), however, are associated with reduction of stroke or major CHD outcomes.[1] The AHA-ASA guidance statement serves as a resource of key contributions of many research groups to the field of VCI.

PATHOGENESIS

VCI can be caused by clinically manifest strokes that may be large or small and of ischemic or hemorrhagic origin.[1] In addition to clinically manifest strokes, VCI may have an underpinning of subclinical cerebrovascular brain injury (CVBI). As a person ages, common vascular brain pathologies include white matter degeneration, primary vessel disease such as arteriolosclerosis and lipohyalinosis, atherosclerosis, cerebral amyloid angiopathy (CAA), and cerebral microbleeds.[1] Cerebral microbleeds at the surface of the brain are thought to be caused by CAA and have been associated with macrohemorrhage of the brain and cognitive impairment.[21]

At the microscopic level of the brain, the neurovascular unit is a conduit for neurovascular dysfunction. The neurovascular unit is made up of neurons,

TABLE 8-1	Key Risk Markers That May Be Linked to Vascular Cognitive Impairment[a]

▶ **Demographic Factors**
Advancing age

▶ **Lifestyle Factors**
Low education
Diet (antioxidants, fish oil, vitamin D, B-complex vitamins, Mediterranean diet, and moderate alcohol consumption of uncertain protective influence)
Lack of physical activity or exercise
Obesity
Smoking habit
Lack of social support/networks

▶ **Depression (Uncertain)**

▶ **Physiologic Factors**
Hypertension
Hyperglycemia, insulin resistance, metabolic syndrome, and diabetes mellitus
Hyperlipidemia (uncertain)

▶ **Concomitant Clinical Vascular Disease**
Coronary artery disease
Stroke
Chronic kidney disease
Atrial fibrillation
Peripheral arterial disease
Low cardiac output

[a] Data from Gorelick PB et al, Stroke.[1] *stroke.ahajournals.org/content/42/9/2672.long.*

glia, and perivascular and vascular cells, and maintains structural and functional homeostasis of the cerebral microenvironment.[1] Vascular oxidative stress and inflammation are believed to be mediators of neurovascular dysfunction induced by traditional vascular risk factors and amyloid-β. A complex interaction ensues between oxidative stress–mediated vascular leakage, protein extravasation, and cytokine production; and inflammation that upregulates expression of reactive oxygen species–producing enzymes and downregulates antioxidant defenses.[1] As a result, with neurovascular dysfunction, the brain's susceptibility to injury increases with altered regulation of cerebral blood supply, disruption of blood-brain barrier function, and potential for reduced trophic support and repair of CVBI. It is hypothesized, therefore, that control of vascular risk factors, reactive oxygen species, and inflammation could lead to preventive or treatment strategies in VCI.[1]

The most common form of VCI is the subcortical type.[22] Cerebral arterial small vessels arise superficially from the subarachnoid circulation as terminations of medium-sized arteries and deeply as arterial perforators from larger vessels at the base of the brain. These vessels supply deep white matter structures, for example, but are not visible by standard neuroimaging. Therefore, their clinical disease signature is white matter disease, lacunar infarcts, and cerebral microbleeds detectable on MRI of the brain.[22] Whereas small cerebral arteries may have pathologic changes such as arteriolosclerosis and CAA, the deep cerebral veins tend to be affected by a process called venous collagenosis, which can also play a role in the pathogenesis of cognitive impairment.

Occlusive disease of deep, small arterial vessels of the brain is believed to lead to lacunar infarcts and a demye-linating disorder of the cerebral white matter referred to as leukoaraiosis (literally, rarefaction or thinning of the white matter). Leukoaraiosis may manifest neuroradiologically on brain CT or MRI as slight, moderate, or severe intensity. White matter changes and lacunar infarcts are correlated and have been associated with cognitive impairment.[22]

Stroke-related factors that can be identified on brain imaging or at brain necropsy—such as volume of cerebral tissue loss, infarct location (eg, strategically located brain infarction in the thalamus, angular gyrus, or subfrontal pathways), infarct number, presence of cerebral atrophy, presence of white matter lesions or volume of these lesions, and silent cerebral infarcts—are commonly believed to indicate risk for VCI.[1] With sophisticated neuroimaging tools such as diffusion tensor imaging, tractography, functional MRI and voxel-based morphometry, researchers are discovering new structural and functional alterations that can occur in the brains of people with stroke and cognitive impairment. Regional white matter integrity (whether on the side of a recent acute CVBI or not) and thalamic density have been suggested as possible pathogenetic links for risk of VCI based on diffusion tensor imaging and voxel-based morphometry study, respectively.[23,24] Furthermore, imaging studies are clarifying the possible roles of the blood glucose level and infarcts of the hippocampus as causal pathways whereby memory decline may occur in the dentate gyrus subregion, based on blood glucose level, whereas the CA1 subregion has been linked to infarction associated with hypoperfusion and cognitive impairment.[25] Finally, microinfarcts of the brain diagnosed at necropsy have been shown to be associated with brain atrophy and cognitive impairment even before dementia manifests clinically.[26]

CLINICAL FEATURES

The clinical picture of patients with VCI may be linked with the volume and location of the underlying pathology. If there is clinical stroke, the location, number, and volume of the stroke(s) determine the pattern and extent of cognitive impairment and behavior change. Juxtaposed with the focal features of specific stroke-related lesions is the more diffuse pattern of cognitive impairment associated with subcortical CVBI. This pattern is marked by slowed mentation (bradyphrenia), executive dysfunction, memory deficits marked by inconsistent acquisition rather than rapid forgetting, and mood disturbance.[27] Individual patients may show both focal neurocognitive deficits associated with the location of their stroke lesions and a more diffuse pattern, depending on the presence and extent of subcortical CVBI.

Two specific cognitive domains deserve special mention: executive function (which refers to higher cognitive skills such as planning, organizing, and synthesizing) and memory. Although many clinicians consider deficits in executive function to be a hallmark of VCI, such deficits are not specific to cerebrovascular disease.[28] Given the lack of clarity of this research, and the fact that many elderly patients with dementia and cognitive impairment have multiple sources of brain pathology,[12] clinicians should be cautious about basing their clinical diagnosis solely on the pattern of cognitive deficits. Memory is a second important cognitive domain. The NINDS-AIREN criteria for VaD require memory impairment.[2] However, perhaps in fear of the "Alzheimerization" of all dementia, subsequent groups of VCI investigators have argued that memory impairment should not be required,[29] and the AHA-ASA criteria do not require it for the diagnosis of VaD or VaMCI.[1] Still, memory impair-

ment is common in patients with VCI.[27] The pattern of memory impairment in VCI can be qualitatively different from that of AD in that a rapid forgetting of newly learned information may not be seen. Instead, patients with cerebrovascular disease are often inefficient in their encoding of the new information, resulting in less information acquired.

Depression is the most common post-stroke psychiatric disturbance, with approximately one-third of patients experiencing depression in the months following their stroke.[30] Also, there may be important vascular contributions to late-life depression or so-called vascular depression.[31] For these reasons, it is important to screen for depressive symptoms in patients with suspected CVBI. Commonly used screening tests in patients with suspected VCI include the geriatric depression scale, the Beck Depression Inventory, and the Center for Epidemiologic Studies Depression Scale. Other neurobehavioral disorders associated with stroke and cerebrovascular disease include dysexecutive behavior and apathy or abulia. Consultation with psychiatry or another health care provider with expertise in neurobehavioral disorders may assist in treatment of patients with post-stroke behavior disturbance.

A review of the pivotal clinical trials in VaD reveals inconsistent demonstrations of global functional improvement in relation to assessment of functional behavior in VCI.[32,33] Reliably differentiating functional disability due to physical (eg, hemiparesis) versus cognitive and behavioral impairment is a specific difficulty in examining for impaired activities of daily living after stroke. The Barthel Index is one of the most popular functional outcome measures used with stroke patients but can be unreliable in older patients, especially those with cognitive impairment. By contrast, the Disability Assessment for Dementia

scale, with its separate scores for initiation, planning, and performance of activities, is better equipped to distinguish between physical and cognitive disability in VCI. Finally, several studies have shown that executive function tests best predict decline in instrumental activities in daily living in both AD and VaD.[34]

PREVENTION AND TREATMENT OF VCI
Prevention

As previously mentioned, prospects for prevention of VCI by risk factor modification have been summarized in a recently published AHA-ASA guidance statement.[1] Key recommendations from this work are summarized in **Table 8-2**.[1] In interpreting the information in

Table 8-2, one should keep in mind that a relatively limited number of highest-evidence studies are available, and the studies are graded based on the level of evidence (ie, estimate of certainty [precision] of the treatment strategy's effect) and class of evidence (ie, size of the treatment strategy's effect) according to an AHA-ASA grading scheme (see reference 1). Terms such as *recommended*, *reasonable*, *may be reasonable*, and *not recommended* are used to guide the clinician based on level and class of evidence, with *recommended* being the highest level of recommendation for a treatment strategy in this grading scheme.

In this review, treatment of hypertension received the highest evidence-based

---

TABLE 8-2 **Key Recommendations for Prevention of Vascular Cognitive Impairment in People at Risk[a]**

Factors	Class and Level of Evidence	Prevention Designations
Lifestyle factors		
Smoking cessation	Class IIa, level of evidence (LOE) A	Reasonable strategy
Moderation of alcohol intake	Class IIb, LOE B	May be a reasonable strategy
Weight control	Class IIb, LOE B	May be a reasonable strategy
Physical activity	Class IIb, LOE B	May be a reasonable strategy
Use of antioxidants and B vitamins	Class III, LOE A	Not beneficial
Physiologic factors		
Treatment of hypertension	Class I, LOE A	Recommended strategy
Treatment of hyperglycemia[b]	Class IIb, LOE C	May be a reasonable strategy
Treatment of hypercholesterolemia[b]	Class IIb, LOE B	May be a reasonable strategy
Treatment of inflammation	Class IIb, LOE C	Uncertain strategy
Other interventions in relation to cognitive decline or impairment		
Mediterranean diet	Class IIb, LOE B	Recommended strategy
Vitamin supplementation	Class IIb, LOE B	Not proven, even if homocysteine levels have been positively modified, or of uncertain usefulness
Physical activity	Class IIb, LOE B	May be considered
Antiaggregant therapy	Class IIb, LOE B	Not well established

[a] Data from Gorelick PB et al, Stroke.[1] *stroke.ahajournals.org/content/42/9/2672.long*.
[b] The effectiveness of treatment of diabetes or hyperglycemia for the prevention of dementia has not been well established (Class IIb, LOE C), and the treatment of hyperlipidemia for the prevention of dementia remains uncertain (Class IIb, LOE C).

---

grade for the prevention of VCI: treating hypertension was recommended for people at risk of VCI (Class I, Level of Evidence [LOE] A recommendation), and in people with a history of stroke, lowering blood pressure was deemed to be an effective means to reduce the risk of post-stroke dementia (Class I, LOE B).[1] There was reasonable evidence to suggest blood pressure–lowering therapy as a useful intervention for people who were middle-aged and younger elderly (Class IIa, LOE B); however, the usefulness of lowering blood pressure for those over 80 years of age for the prevention of dementia was not well established (Class IIb, LOE B).[1] See **Table 8-2** for management recommendations of other risk markers or factors.

A recently published NIH Consensus Panel work on reducing risk of AD or cognitive decline in older people concluded that the quality of evidence was generally low and inadequate to determine that therapeutic interventions would be able to delay the onset of AD or reduce cognitive decline.[35] Further robust and consistent studies are necessary to provide clear, concise answers to important research questions regarding the role of vascular risks for cognitive impairment and dementia.[36]

Treatment

Many treatments have been tried for VCI, but none have proven unequivocally to be efficacious and safe.[37,38] At one time, it was thought that control of blood pressure in the range of 135 to 150 mm Hg might be useful to maintain cognitive function in people with hypertension and VCI, and that aspirin therapy might be useful to improve cerebral perfusion, cognitive performance, quality of life, and independence. Currently, however, no drugs that have gained wide acceptance for use in practice have been approved by the US Food and Drug Administration for the treatment of VCI.

More recently, attention has turned to cholinesterase inhibitors according to the rationale that cholinergic pathways from the nucleus basalis of Meynert may be disrupted by subcortical cerebrovascular disease and there may be mixed AD and VCI.[38] In large VCI clinical trials of the cholinesterase class of drugs, the key findings show inconsistent benefits across primary or other key end points, or an effect that may be primarily limited to those with mixed AD plus VCI.[32,40–42] A similar result was noted with the administration of donepezil in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a genetic model of subcortical VCI, as the primary end point of the trial was not realized; however, measures of executive function were improved (**Case 8-2**).[44] The failure of the cholinesterase inhibitors to successfully treat patients with VaD on an across-the-board cognitive and functional basis has raised questions regarding whether there is an absence of cholinergic deficits in pure VaD.[45]

Memantine, an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, has statistically significantly improved cognitive outcome in some key cognitive study end points in large trials.[33] Nimodipine showed similar results for influencing cognitive function.[46]

Overall, the various treatment modalities reviewed above do not provide consistent cognitive and functional benefit. Keeping this feature in mind, the following are recommendations for drug treatments of VCI in an evidence-based guidance statement in collaboration with the AHA-ASA:[1]

1. Donepezil may be useful for improving cognition in patients with VaD (Class IIa, LOE A).
2. Galantamine may be useful for patients with mixed AD/VaD (Class IIa, LOE A).

KEY POINTS

- There is reasonable evidence to suggest blood pressure–lowering therapy as a useful intervention for people who are middle-aged and younger elderly (Class IIa, Level of Evidence B); however, the usefulness of lowering blood pressure for those over 80 years of age for the prevention of dementia is not well established (Class IIb, Level of Evidence B).

- Further robust and consistent studies are necessary to provide clear, concise answers to important research questions regarding the role of vascular risks for cognitive impairment and dementia.

- Currently no drugs that have gained wide acceptance for use in practice have been approved by the US Food and Drug Administration for the treatment of vascular cognitive impairment.

- The failure of the cholinesterase inhibitors to successfully treat patients with vascular dementia on an across-the-board cognitive and functional basis has raised questions regarding whether there is an absence of cholinergic deficits in pure vascular dementia.

Case 8-2

A 67-year-old woman was transferred to the inpatient stroke unit with a diagnosis of possible vasculitis. She had a medical history of hypertension and unexplained left-side weakness and slight gait difficulty at age 38, from which she had recovered almost completely. Her daughter described the patient's cognition as ''not quite normal'' from that time onward and said that it had worsened slightly over time with periods of confusion, which the family blamed on her frequent headaches. Several days before her transfer to the stroke unit, the patient developed slurred speech and weakness of the right face, arm, and leg. She was treated at the referral hospital with IV steroids, as she had waxing and waning mental status in addition to the right-side weakness. Physical examination in the stroke unit showed slight left arm and leg weakness and rather profound right face, arm, and leg weakness with dysarthria. The brain MRI (**Figure 8-2** and **Figure 8-3**) performed at the referral hospital showed prominent white matter disease with involvement of the external capsule and possible early involvement of the temporal lobe tips. In addition, diffusion-weighted image showed a left periventricular signal consistent with a small, deep acute infarction.

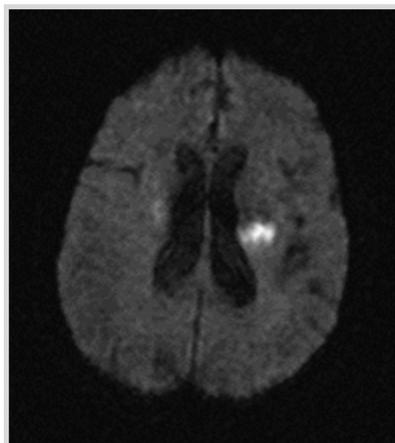Results of a lumbar puncture performed at the stroke unit upon her arrival showed a slight elevation in the protein content, but all other parameters were unremarkable, including a 14-3-3 protein study. Blood study results for prothrombotic states were unremarkable, as were sedimentation rate, a high-sensitivity C-reactive protein test, and a panel for collagen-vascular abnormalities. Conventional cerebral angiography showed several areas of possible vasculitic changes, but the neuroradiologist was not fully convinced of

FIGURE 8-2 Diffusion-weighted brain MRI. Note increased signal intensity of periventricular area on the left side.

FIGURE 8-3 Brain MRI. Note extensive white matter disease with involvement of external capsule. Other MRI sequences showed slight involvement of the temporal tips bilaterally.
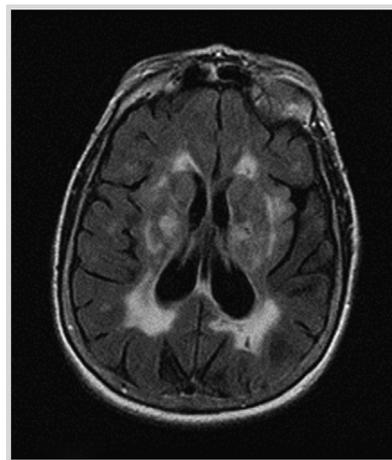
the findings. After the conventional cerebral angiography study, and at the urging of the family members, the patient had a leptomeningeal-brain biopsy, which did not show evidence of a vasculitic process.

Comment. The brain MRI findings are consistent with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a monogenetic disorder mapped to chromosome 19q12.[43] CADASIL typically begins in early adulthood; symptoms comprise migraine with aura, mood disturbance, recurrent strokes, cognitive impairment, and extensive white matter disease. Most cases have a missense mutation of the Notch 3 gene and ultrastructural changes in skin and muscle vessels including granular osmophilic material in the arteriolar media. Because CADASIL is an autosomal dominant disorder, it is important to discuss screening other members of a patient's immediate family. There is no definitive prevention or treatment, and many cases go on to develop significant cognitive impairment.

Notch 3 gene mutation study was obtained on the serum of this patient and was consistent with a diagnosis of CADASIL, as was the brain biopsy electron microscopy study.

3. The benefits of rivastigmine and memantine are not well established.

Cholinesterase inhibitors have been shown to benefit cognition and may also improve behavior and ability to perform activities of daily living more than placebo therapy in some forms of dementia such as AD or VCI.[39] However, a systematic review of pharmacologic treatment of neuropsychiatric symptoms associated with dementia suggests that such therapies are not particularly effective and can be complicated by increased risk of some types of cardiovascular disease, such as stroke.[47] A review of the management of noncognitive symptoms in dementia by Drs Burke, Hall, and Tariot can be found in this **CONTINUUM** issue.

Finally, although aspirin has not been conclusively shown to benefit cognitive function in people at risk,[48] there is an ongoing, large-scale trial (Aspirin for Reducing Events in the Elderly) for the primary prevention of major adverse cardiovascular events and VaD,[49] and an ongoing systolic blood pressure–control study (the Systolic Blood Pressure Intervention Trial—Memory and Cognition in Decreased Hypertension, commonly referred to as SPRINT-MIND) to discern the influence of blood pressure control on cognitive function).[50]

REFERENCES

1. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42(2):2672–2713.

2. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993; 43(2):250–260.

3. Hachinski V. Stroke and Alzheimer disease. fellow travelers or partners in crime? Arch Neurol 2011;68(6):797–798.

4. Hachinski V. World Stroke Day 2008. ''Little strokes, big trouble''. Stroke 2008;39(9): 2407–2408.

5. Fratiglioni L, Launer LJ, Andersen K, et al. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;54(11 suppl 5):S10–S15.

6. Andersen K, Launer LJ, Dewey ME, et al. Gender differences in the incidence of AD and vascular dementia: The EURODEM Studies. EURODEM Incidence Research Group. Neurology 1999;53(9):1992–1997.

7. Ivan CS, Seshardri S, Beiser A, et al. Dementia after stroke: the Framingham Study. Stroke 2004;35(6):1264–1269.

8. Zhang Z-X, Zahner GEP, Roman GC, et al. Dementia subtypes in China: prevalence in Beijing, Xian, Shanghai, and Chengdu. Arch Neurol 2005;62(3):447–453.

9. Yamada M, Mimori Y, Kasagi F, et al. Incidence of dementia, Alzheimer disease, and vascular dementia in a Japanese population: Radiation Effects Research Foundation adult health study. Neuroepidemiology 2008;30(3):152–160.

10. Honig LS, Tang M-X, Albert S, et al. Stroke and the risk of Alzheimer disease. Arch Neurol 2003;60(12):1707–1712.

11. Bennett DA, Schneider JA, Bienias JL, et al. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. Neurology 2005;64(5): 834–841.

12. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69(24):2107–2204.

13. Mitchell SL, Teno JM, Keily DK, et al. The clinical course of advanced dementia. N Engl J Med 2009;361(16):1529–1538.

14. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 2010;304(16): 1787–1794.

15. Freels S, Nyenhuis D, Gorelick PB. Predictors of survival in African American patients with AD, VaD, or stroke without dementia. Neurology 2002;59(8):1146–1153.

16. Gorelick PB, Brody J, Cohen D, et al. Risk factors for dementia associated with multiple cerebral infarcts. A case-controlled analysis in predominantly African-American hospital-based patients. Arch Neurol 1993; 50(7):714–720.

17. Gorelick PB, Freels S, Harris Y, et al. Epidemiology of vascular and Alzheimer's dementia among African Americans in Chicago, IL: baseline frequency and comparison of risk factors. Neurology 1994; 44(8):1391–1396.

18. Pytel P, Cochran EJ, Bonner G, et al. Vascular and Alzheimer-type pathology in an autopsy study of African-Americans. Neurology 2006;66(3):433–435.

19. Gorelick PB. Cerebral microbleeds: evidence of heightened risk associated with aspirin use. Arch Neurol 2009;66(6):691–693.

20. Gorelick PB, William M. Feinberg Lecture: cognitive vitality and the role of stroke and cardiovascular disease risk factors. Stroke 2005;36(4):875–879.

21. Grysiewicz R, Gorelick PB. Update on amyloid-associated intracerebral hemorrhage. Eur Neurol Rev 2012;7:22–24.

22. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010; 9(7):689–701.

23. Stebbins GT, Nyenhuis DL, Wang C, et al. Gray matter atrophy in patients with ischemic stroke with cognitive impairment. Stroke 2008;39(3):785–793.

24. Wang C, Stebbins GT, Nyenhuis DL. Longitudinal changes in white matter following ischemic stroke: a three-year follow-up study. Neurobiol Aging 2006;27(12):1827–1833.

25. Wu W, Brickman AM, Luchsinger J, et al. The brain in the age of old: the hippocampal formation is targeted differentially by diseases of late life. Ann Neurol 2008;64(6): 698–706.

26. Launer LJ, Hughes TM, White LR. Microinfarcts, brain atrophy, and cognitive function: the Honolulu Asia Aging Study Autopsy Study. Ann Neurol 2011;70(5): 774–780.

27. Nyenhuis DL, Gorelick PB, Geenen EJ, et al. The pattern of neuropsychological deficits in Vascular Cognitive Impairment-No Dementia (Vascular CIND). Clin Neuropsychol 2004; 18(1):41–49.

28. Marchant NL, Reed BR, DeCarli CS, et al. Cerebrovascular disease, beta-amyloid, and cognition in aging. Neurobiol Aging 2012; 33(5):1006.e25–e36.

29. Hachinski V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke 2006;37(9): 2220–2241.

30. Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke: a systematic review of observational studies. Stroke 2005;36(6):1330–1340.

31. Bella R, Pennisi G, Cantone M, et al. Clinical presentation and outcome of geriatric depression in subcortical ischemic vascular disease. Gerontology 2010;56(3):298–302.

32. Black S, Roman GC, Geldmacher DS, et al. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized placebo-controlled trial. Stroke 2003;34(10):2323–2332.

33. Orgogozo J-M, Rigaud A-S, Stoffler A, et al. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). Stroke 2002;33(7): 1834–1839.

34. Cahn-Weiner DA, Farias ST, Julian L, et al. Cognitive and neuroimaging predictors of instrumental activities of daily living. J Int Neuropsychol Soc 2007;13(5):747–757.

35. Daviglus ML, Bell CC, Berrettini W, et al. National Institutes of Health State-of-the-Science Conference statement: preventing Alzheimer disease and cognitive decline. Ann Intern Med 2010;153(3): 176–181.

36. Pantoni L, Gorelick PB. Advances in vascular cognitive impairment 2010. Stroke 2011; 42(2):291–293.

37. European Pentoxifylline Multi-Infarct Dementia Study. Eur Neurol 1996;36(6): 315–321.

38. Marcusson J, Rother M, Kittner B, et al. A 12-month, randomized placebo-controlled trial of propentofylline (HWA 285) in patients with dementia according to DSM III-R. The European Propentofylline Study Group. Dement Geriatr Cogn Disord 1997;8(5): 320–328.

39. Farlow MR. Use of antidementia agents in vascular dementia: beyond Alzheimer disease. Mayo Clin Proc 2006;81(10): 1350–1358.

40. Roman GC, Wilkinson DG, Doody RS, et al. Donepezil in vascular dementia: combined analysis of two large-scale clinical trials. Dement Geriatr Cogn Disord 2005;20(6): 338–344.

41. Erkinjuntti T, Kurz A, Gauthier S, et al. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet 2002;359(9314): 1283–1290.

42. Auchus AP, Brashear HR, Salloway S, et al. Galantamine treatment of vascular dementia: a randomized trial. Neurology 2007;69(5): 448–458.

43. Gorelick PB. CADASIL: do the clinical and MRI profiles differ for women and men? Stroke 2012;43(1):8–10.

44. Dichgans M, Markus HS, Salloway S, et al. Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. Lancet Neurol 2008;7(4):310–318.

45. Perry E, Ziabreva I, Perry R, et al. Absence of cholinergic deficits in ''pure'' vascular dementia. Neurology 2005;64(1):132–133.

46. Pantoni L, del Ser T, Soglian AG, et al. Efficacy and safety of nimodipine in subcortical vascular dementia: a randomized placebo-controlled trial. Stroke 2005;36(3): 619–624.

47. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA 2005;293(5):596–608.

48. Price JF, Stewart MC, Deary IJ, et al. Low dose aspirin and cognitive function in middle aged to elderly adults: randomized controlled trial. BMJ 2008;337:a1198.

49. Nelson MR, Reid C, Beilin LJ, et al. Rationale for a trial of low-dose aspirin for the primary prevention of major adverse cardiovascular events and vascular dementia in the elderly: Aspirin in Reducing Events in the Elderly (ASPREE). Drugs Aging 2003; 20(12):897–903.

50. NIH News. NIH launches multicenter clinical trial to test blood pressure strategy. *http://public.nhlbi.nih.gov/newsroom/home/ GetPressRelease.aspx?od=2667*. Accessed November 2, 2009.