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Vascular Cognitive Impairment

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ABSTRACT

Purpose of Review: This article provides a diagnostic framework for vascular cognitive impairment, discusses prevalence and relationships to other neurodegenerative pathologies, and provides advice on diagnostic workup and management.

Recent Findings: Vascular cognitive impairment is the second most common cause of cognitive impairment and frequently coexists with other neurodegenerative neuropathologies. Three new diagnostic criteria have been published recently; common diagnostic elements include the need to classify cognitive impairment as mild cognitive impairment or dementia and to link the cognitive impairment to evidence of clinically significant cerebrovascular disease. Vascular cognitive impairment may be further subclassified into poststroke vascular cognitive impairment and nonstroke vascular cognitive impairment, most commonly caused by cerebral small vessel disease, which may only be recognized on neuroimaging.

Summary: Vascular cognitive impairment is a potentially treatable common cause of cognitive impairment, progression of which may be slowed or halted by secondary prevention of vascular disease.

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INTRODUCTION

Vascular cognitive impairment is the second most common cause of dementia and may be the most preventable and treatable cause. Vascular cognitive impairment is commonly encountered in two forms. In poststroke vascular cognitive impairment, the cognitive impairment is the immediate and direct consequence of a symptomatic stroke. In nonstroke-related vascular cognitive impairment, the cognitive impairment is the consequence of clinically hard-to-detect cerebrovascular disease, which may be evident only on neuroimaging with CT or MRI. Additionally, vascular cognitive impairment is a frequent contributor to mixed dementia, accompanied by other neuropathologies such as Alzheimer pathology. This article summarizes the classification, diagnosis, and management of vascular cognitive impairment.

CLASSIFICATION OF VASCULAR COGNITIVE IMPAIRMENT

Classification criteria for vascular cognitive impairment have been published by the *International Classification of Diseases, Tenth Revision (ICD-10)*,¹ National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN),² State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC),³ American Heart Association/American Stroke Association (AHA/ASA),⁴ the International Society of Vascular Behavioural and Cognitive Disorders (Vas-Cog),⁵ and in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*⁶ and *Fifth Edition (DSM-5)*.⁷

Common elements of recent criteria are given in **Table 6-1**. All of these classification schemes require that some



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TABLE 6-1 Recent Classification Criteria for Vascular Cognitive Impairment

	AHA/ASA⁴	Vas-Cog Society⁵	DSM-5⁷
Cognitive criteria	Discriminates between vascular mild cognitive impairment and vascular dementia	Discriminates between mild and major vascular cognitive disorder (dementia)	Discriminates between mild and major vascular neurocognitive disorder
Criteria for probable vascular cognitive impairment	<p>There is imaging evidence of cerebrovascular disease and either:</p> <p>There is a clear temporal relationship between a vascular event (eg, clinical stroke) and onset of cognitive deficits.</p> <p>OR</p> <p>There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology.</p> <p>There should be no history of gradually progressive cognitive deficits before or after stroke that suggest the presence of a nonvascular cognitive disorder (eg, Alzheimer disease).</p>	<p>Either:</p> <p>The onset of cognitive deficits follows one or more strokes or there are physical signs consistent with stroke.</p> <p>OR</p> <p>If history of stroke or transient ischemic attack is absent, then there is evidence of cognitive decline in speed of information processing, complex attention or frontal executive functions, accompanied by one or more of: gait disturbances, urinary symptoms, or personality and mood changes.</p> <p>There should be neuroimaging evidence of either large vessel infarct, strategically placed single infarct(s) or intracerebral hemorrhages(s), multiple (more than two) lacunar infarcts outside the brainstem, or extensive and confluent white matter lesions.</p> <p>There should not be evidence of other nonvascular cognitive, medical, psychiatric, or neurologic disorders sufficient to explain the cognitive impairment (including Alzheimer disease).</p>	<p>The criteria are met for major or mild neurocognitive disorder.</p> <p>The clinical features are consistent with a vascular etiology, as suggested by either of the following:</p> <p>Onset of the cognitive deficits is temporally related to one or more cerebrovascular events.</p> <p>OR</p> <p>Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function.</p> <p>There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits.</p> <p>The symptoms are not better explained by another brain disease or systemic disorder.</p> <p>Probable vascular neurocognitive disorder is diagnosed if one of the following is present; otherwise possible vascular neurocognitive disorder should be diagnosed:</p> <p>Clinical criteria are supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease (neuroimaging supported).</p>

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TABLE 6-1 Recent Classification Criteria for Vascular Cognitive Impairment *Continued from page 491*

	AHA/ASA ⁴	Vas-Cog Society ⁵	DSM-5 ⁷
			OR The neurocognitive syndrome is temporally related to one or more documented cerebrovascular events. OR Both clinical and genetic (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) evidence of cerebrovascular disease is present.
Criteria for possible vascular cognitive impairment	Meets criteria except that there is no clear relationship between the vascular disease and the cognitive impairment, there is insufficient information (eg, neuroimaging studies are not available), severe aphasia precludes accurate cognitive assessment, or there is evidence of other neurodegenerative conditions (eg, Alzheimer disease) in addition to cerebrovascular disease.	Meets criteria except that neuroimaging is not available.	Clinical criteria are met but neuroimaging is not available and the temporal relationship of the neurocognitive syndrome with one or more cerebrovascular events is not established.
Classification when other potential causes are present (ie, mixed disease)	Possible vascular mild cognitive impairment or dementia should be diagnosed when there is evidence of other neurodegenerative conditions.	Vascular mild/major cognitive disorder with concomitant Alzheimer disease may be diagnosed when the patient additionally meets criteria for probable or possible AD.	Not specifically addressed.

AHA/ASA = American Heart Association/American Stroke Association; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; Vas-Cog = International Society of Vascular Behavioural and Cognitive Disorders.

degree of cognitive impairment should be present along with evidence—from some combination of history, physical examination, cognitive profile, and diagnostic testing, including neuroimaging—of a vascular contribu-

tion to the cognitive impairment. The term vascular cognitive impairment is intended to encompass all forms of cognitive impairment, not only dementia, and to include all cases where vascular disease contributes to impairment,

including in cases where it is not the sole contributor. More recent classification systems—the AHA/ASA, Vas-Cog, and *DSM-5*—distinguish between vascular mild cognitive impairment (MCI) (or minor vascular neurocognitive disorder in the *DSM-5*) and vascular dementia (or major vascular neurocognitive disorder in the *DSM-5*).

AHA/ASA and Vas-Cog criteria further classify vascular cognitive impairment as probable or possible based on the completeness of the diagnostic workup and the presence or absence of evidence for competing causes of dementia, such as Alzheimer disease (AD). In practice, probable vascular cognitive impairment may be the minority of cases because comorbid pathologies such as AD are commonly identified, or at least cannot be ruled out with certainty.

AHA/ASA, Vas-Cog, and *DSM-5* criteria acknowledge that vascular cognitive impairment may come in the form of poststroke vascular cognitive impairment or nonstroke forms of vascular cognitive impairment, such as that caused by subcortical ischemic disease. This distinction is important as it makes clear that the absence of a clinical history of stroke does not exclude vascular cognitive impairment. Indeed, neuroimaging and neuropathology studies have established that clinically silent, or “covert,” cerebrovascular disease becomes extremely common with aging, is associated with cognitive impairment and the presence of dementia, and is sufficient to cause clinically relevant cognitive impairment.

Furthermore, Vas-Cog criteria subclassify vascular cognitive impairment according to cerebrovascular pathology (Table 6-2). It is important to recognize that the vascular pathologies underlying vascular cognitive impairment are extremely diverse (including arteriosclerosis, cerebral amyloid angiopathy,

atheroembolism, cardiac embolism, hypoperfusion, and hemorrhage) such that patient prognosis and management must be highly individualized. With appropriate case-specific management of the vascular risk factors relevant to the patient’s vascular pathology, it may be possible to arrest progression of vascular cognitive impairment by preventing further cerebrovascular injury.

DIAGNOSIS AND DIAGNOSTIC TESTING

The diagnosis of a patient with possible vascular cognitive impairment may be considered to consist of three stages. First, a determination should be made of whether evidence of cognitive impairment exists, including classification as MCI or dementia. Second, a workup for the presence of vascular disease should be completed, including its location, severity and underlying causes, and risk factors. Third, consideration should be given as to whether the vascular disease is sufficient to partly or wholly explain the cognitive impairment.

Assessing Cognitive Impairment in Vascular Cognitive Impairment

The assessment for cognitive impairment should follow the same principles for assessment of MCI and dementia as provided in the article “The Mental Status Examination in Patients With Suspected Dementia” by Murray Grossman, MD, FAAN, and David J. Irwin, MD,⁸ and in the article “Mild Cognitive Impairment” by Ronald C. Petersen, PhD, MD,⁹ in this issue of *Continuum*. The sensitivity for detecting vascular cognitive impairment is enhanced by the use of screening or assessment tools that interrogate executive function and

KEY POINTS

- Diagnostic criteria for vascular cognitive impairment are based on the presence of cognitive impairment and vascular disease as well as a clinical judgment that the vascular disease is causing the impairment.
- The term vascular cognitive impairment encompasses all severity of cognitive impairment caused by vascular disease, including mild cognitive impairment and dementia.
- Vascular cognitive impairment may be subclassified as poststroke vascular cognitive impairment, which refers to the direct immediate consequence of clinical stroke, or as nonstroke vascular cognitive impairment, which is most commonly caused by cerebral small vessel disease.
- Vascular cognitive impairment has many vascular causes. The cause of the vascular disease should be identified so that further progression or recurrence can be prevented.

KEY POINT

■ The clinical assessment for vascular cognitive impairment can be conceived as a three-stage process that includes the following steps: (1) assess for cognitive impairment; (2) assess the presence, severity, and cause of vascular disease; and (3) assess whether the vascular disease is sufficient to cause the impairment, in whole or in part.

TABLE 6-2 Vascular Pathology of Vascular Cognitive Impairment^a
► Parenchymal Lesions of Vascular Etiology

Large vessel atherothromboembolic disease

Multiple infarcts

Single strategically placed infarct

Small vessel disease

Multiple lacunar infarcts

Ischemic white matter damage

Dilated perivascular spaces

Microinfarcts

Microhemorrhages

Hemorrhage

Intracerebral hemorrhage

Multiple microbleeds

Subarachnoid hemorrhage

Hypoperfusion

Hippocampal sclerosis

Laminar cortical necrosis

► Types of Vascular Pathologies

Atherosclerosis

Cardiac, atherosclerotic, and systemic emboli

Arteriolosclerosis

Lipohyalinosis

Cerebral amyloid angiopathy

Vasculitis

Venous collagenosis

Arteriovenous fistulae

Hereditary angiopathies (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL])

Berry aneurysms

Miscellaneous vasculopathies (eg, moyamoya disease)

Cerebral venous thrombosis

^a Modified with permission from Sachdev P, et al, Alzheimer Dis Assoc Disord.⁵ journals.lww.com/alzheimerjournal/Abstract/2014/07000/Diagnostic_Criteria_for_Vascular_Cognitive.2.aspx. © 2014 Lippincott Williams & Wilkins.

processing speed, which are frequently affected in patients with vascular cognitive impairment. For example, the Montreal Cognitive Assessment (MoCA) tool appears to be a more sensitive tool for vascular cognitive impairment than the Mini-Mental State Examination (MMSE), attributed to the relatively greater degree of executive function assessment on the MoCA (www.mocatest.org).^{10,11} When clinical uncertainty persists despite the use of a validated bedside cognitive screening tool, neuropsychological testing is often helpful. The cognitive profile of vascular cognitive impairment is further described later in this article.

Assessing the Presence of Cerebrovascular Disease in Patients With Vascular Cognitive Impairment

The determination of the presence of cerebrovascular disease may be based on a combination of history, examination, and diagnostic testing such as neuroimaging. The clearest evidence of cerebrovascular disease is when a clinical history of stroke exists. However, the physician should be sure that the diagnosis of stroke is well supported by clinical history, medical records, physical examination showing neurologic signs consistent with past stroke (such as aphasia, dysarthria, hemianopia, or other focal neurologic signs) and, if needed or available from previous stroke workup, neuroimaging evidence of cerebral infarction or hemorrhage consistent with the signs and symptoms. Patient-reported history of stroke is generally reliable; however, nonspecific neurologic symptoms can sometimes be falsely reported as stroke, introducing diagnostic confusion.

Identifying the presence of cerebrovascular disease is more difficult

when a history of stroke is absent. Neuroimaging can identify evidence of silent strokes and other manifestations of cerebral small vessel disease that are hard to detect clinically. Clinical history, signs, and symptoms may be suggestive of nonstroke vascular cognitive impairment but are not highly sensitive or specific and should not be relied on to diagnose vascular cognitive impairment in the absence of neuroimaging confirmation. These signs and symptoms include frontal gait disorder, urinary incontinence, a stepwise progression of cognitive impairment with intervening static periods, prominent executive dysfunction and slowed processing speed on neuropsychological testing, and minor asymmetric neurologic signs such as increased tone, reflex asymmetry, Babinski responses, or frontal release signs.⁵ The presence of vascular risk factors such as diabetes mellitus and hypertension should increase suspicion for vascular cognitive impairment but should not be taken as proof of its presence.

Neuroimaging is recommended by the AHA/ASA as helpful for the diagnosis of vascular cognitive impairment.⁴ Neuroimaging is useful not only for identifying the presence of cerebrovascular disease, but also the location and severity of the cerebrovascular lesions, which help determine the clinical significance of the lesions, including whether they are sufficient to account for the cognitive impairment. MRI is superior to CT for identifying small infarcts and hemorrhages and demonstrates more manifestations of cerebral small vessel disease; therefore, MRI should be preferred over CT.¹² In patients with a history of stroke, neuroimaging should generally identify the previous infarct or hemorrhage unless it is small. In patients with cerebral small vessel disease, MRI may identify a range of

KEY POINTS

- Cerebrovascular disease should be diagnosed by history, examination, and diagnostic testing, including neuroimaging.
- Neuroimaging provides useful evidence of the presence, location, and severity of cerebrovascular disease.

KEY POINT
■ Because cerebrovascular disease is common and can be incidental, clinical judgment is needed in individual patients to determine whether cerebrovascular lesions are sufficient to cause cognitive impairment in the affected individual.

manifestations, including small infarcts, lacunae of presumed vascular origin, white matter hyperintensities, and others (Figure 6-1). A recent consensus statement offers recommendations for terms, definitions, and reporting of cerebral small vessel disease as a contributor to neurodegeneration.¹²

Assessing the Relationship Between Cerebrovascular Disease and Cognitive Impairment

Determining whether the identified cerebrovascular disease is sufficient to account for, in whole or in part, cognitive impairment may be the most clinically difficult part of the assess-

ment for vascular cognitive impairment. Although general principles relating the location and severity of cerebrovascular disease to the risk for cognitive impairment have been established, there are no objectively derived models or risk scores to predict the presence of cognitive impairment in individual patients based on their clinical characteristics and burden of cerebrovascular disease. Therefore, clinical judgment is required to determine whether identified cerebrovascular disease is clinically relevant, or merely an incidental finding. This judgment is difficult because cerebrovascular disease is a common

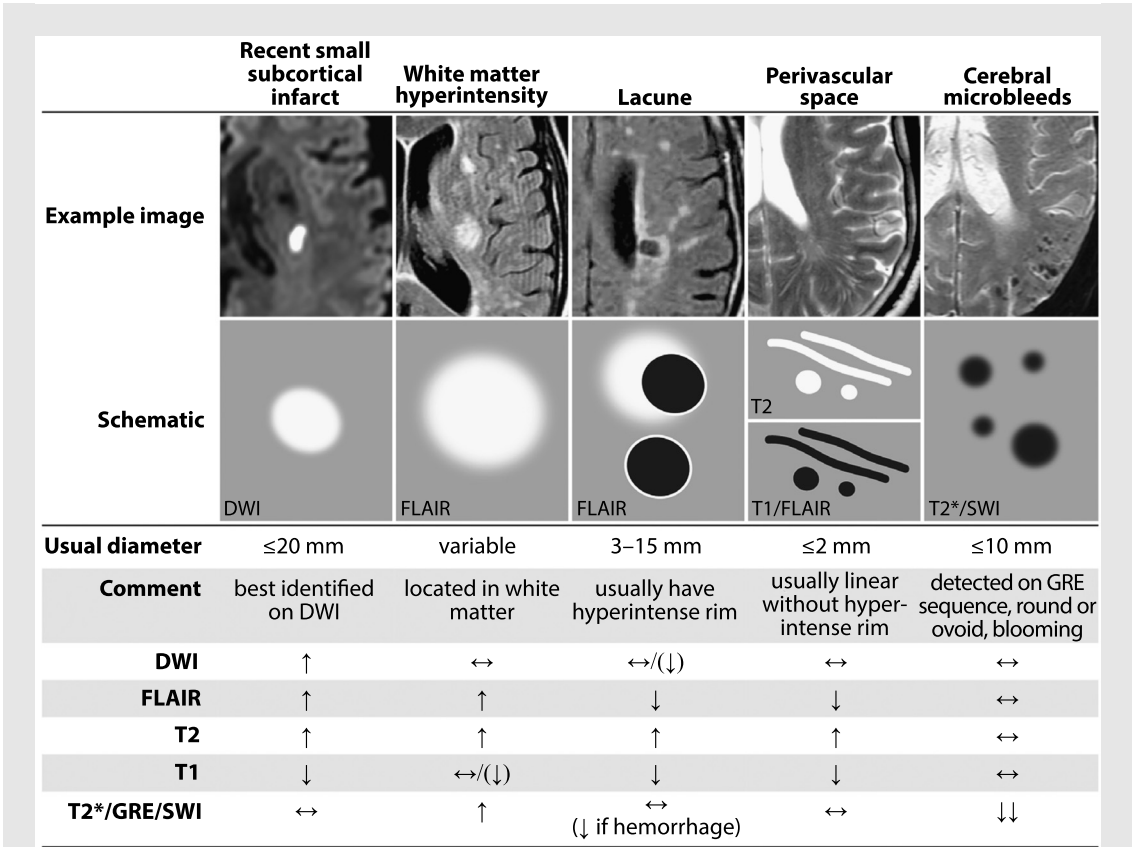


FIGURE 6-1 MRI manifestations of cerebral small vessel disease.
DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; GRE = gradient recalled echo; SWI = susceptibility-weighted imaging.
Reprinted with permission from Wardlaw JM, et al, Lancet Neurol.¹² [www.thelancet.com/journals/lanneu/article/PIIS1474-4422\(13\)70124-8/abstract](http://www.thelancet.com/journals/lanneu/article/PIIS1474-4422(13)70124-8/abstract). © 2013 Elsevier Ltd.

accompaniment of aging that is frequently seen in nonimpaired individuals, as well as in impaired individuals (where it tends to be more severe and diffuse). For example, silent brain infarcts, extensive white matter hyperintensities, and microbleeds, are frequently detected on MRI of older individuals without dementia (Table 6-3).^{14–16}

The clearest circumstance where cerebrovascular disease can be definitively related to cognitive impairment is in poststroke vascular cognitive impairment, where there is a clinical history of stroke, preceded by the absence of cognitive symptoms but immediately followed by cognitive impairment (Case 6-1). In this case, the diagnosis of vascular cognitive impairment is essentially certain. However, a pitfall to avoid is to overlook a history of prestroke cognitive decline, which, if present, could indicate either a competing neurodegenerative cause of dementia or a mixed dementia. Formal questionnaires such

as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)¹⁷ (Supplemental Digital Content 6-1, <http://links.lww.com/CONT/A172>) can be used to assess for prestroke cognitive decline, or a careful clinical history of performance on instrumental activities of living (such as driving, shopping, and handling finances) can be used to screen for prestroke cognitive disabilities.

The number, volume, and location of infarcts or hemorrhages is related to the risk for poststroke cognitive impairment. Single, strategic locations have been identified that are associated with poststroke cognitive impairment when affected by stroke.¹⁸ These locations include left hemisphere perisylvian language areas, the thalamus, midbrain, medial temporal lobe, and medial frontal lobe. Single strokes in these regions can cause cognitive impairment by affecting brain networks sustaining language, attention, or memory. Cognitive impairment may also result from the combined effect

KEY POINT

- In poststroke vascular cognitive impairment, the link between stroke and subsequent vascular cognitive impairment should be readily apparent.

TABLE 6-3 Prevalence of Cerebral Small Vessel Disease on Magnetic Resonance Imaging in the General Population Without Dementia^a

Age Decade	Infarcts		Beginning Confluent or Confluent White Matter Hyperintensities on MRI ^b	Microbleeds ^c	
	≥1 infarct	≥2 infarcts		T2*-Weighted Gradient Recalled Echo (GRE)	Susceptibility-Weighted Imaging (SWI)/ High-Sensitivity Sequence
50–59	5–8%	1–2%	1%	3%	12%
60–69	7–12%	2–3%	1–4%	5–10%	15–17%
70–79	12–23%	3–6%	6–14%	8–16%	30–31%
80+	25–38%	6–9%	19%	18%	40%

MRI = magnetic resonance imaging.

^a Data are aggregated from multiple population-based studies.

^b As measured using the Fazekas scale.¹³

^c As can be seen from the table, susceptibility-weighted imaging (SWI) and other newer, high-sensitivity MRI sequences detect about twice as many microbleeds as older T2*-weighted gradient recalled echo (GRE) sequences.

Case 6-1

A 71-year-old woman presented acutely with confusion, vomiting, left hemianopia, left hemiparesis, and skew deviation. Head CT was unremarkable but CT angiography showed that the basilar artery was occluded due to thrombus formation on an atherosclerotic plaque. The patient was treated with IV tissue plasminogen activator and endovascular thrombectomy. The patient's motor and oculomotor findings resolved after treatment. However, the patient remained cognitively impaired, with deficits in verbal learning and recall. Diffusion-weighted MRI showed acute infarction (bright signal) in the right occipital and bilateral medial temporal lobes (**Figure 6-2**). During follow-up 3 months later, the patient described symptoms of persistent forgetfulness that interfered with shopping, finances, and driving. Poststroke vascular dementia was diagnosed.

Comment. Strategic infarctions in the bilateral medial temporal lobes caused vascular dementia in this case. Poststroke dementia has also been associated with infarcts in locations such as the left perisylvian cortex, medial frontal lobe, or thalamus, or with the presence of multiple cortical infarcts.

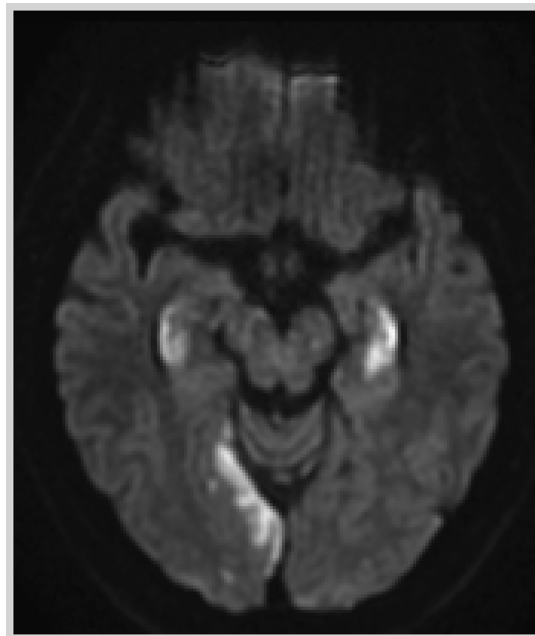


FIGURE 6-2 Axial diffusion-weighted MRI of the patient in **Case 6-1** shows acute infarction (bright signal) in the right occipital and bilateral medial temporal lobes.

KEY POINTS

- Location, as well as size and severity, must be taken into account when considering the cognitive consequences of infarcts and other cerebrovascular lesions.
- The diagnosis of nonstroke vascular cognitive impairment should be supported by the presence of diffuse, severe cerebrovascular disease.

of multiple strokes affecting sufficient brain regions, such as the prefrontal lobes, involved in cognitive processing. This syndrome has been termed multi-infarct dementia. By contrast, the clinician should generally be sceptical of relating cognitive impairment to single, small to moderately sized infarcts in brain regions outside the aforementioned strategic areas for cognitive processing. No single volume threshold reliably discriminates patients with poststroke vascular cognitive impairment versus those without because the cognitive effects of infarcts and hemorrhages depends on the locations of the lesions as well as their size.

Consensus criteria recommend that the diagnosis of nonstroke vascular cognitive impairment should be

based on a pattern of diffuse, severe cerebrovascular disease.^{4,5} In most cases, nonstroke vascular cognitive impairment is caused by subcortical ischemic cerebral small vessel disease, also called Binswanger disease (**Case 6-2**). However, our understanding of the relationship between the location, extent, and severity of the cerebral small vessel disease and the resulting clinical syndromes is still incomplete; therefore, only general principles can be discussed. Silent brain infarcts and white matter hyperintensities on MRI predict risk for dementia in population-based studies, and silent brain infarcts are associated with presence of dementia in autopsy-based studies,^{19–21} while the relationship of cerebral microbleeds to cognition is less clear. Small infarcts in the thalamus

Case 6-2

A 65-year-old man presented with cognitive slowing, forgetfulness, and decreased gait speed that he had experienced for approximately 1 year. He was no longer able to manage his own finances or do his own shopping. He had a history of poorly controlled hypertension. The patient's Montreal Cognitive Assessment (MoCA) score was 14 out of 30. Neurologic examination showed mild hyperreflexia, a few beats of clonus at each ankle, and a slow, unsteady gait with a shortened stride length but nearly normal base width. Brain MRI showed severe white matter hyperintensities with multiple lacunae of presumed vascular origin (**Figure 6-3**). A diagnosis of probable vascular dementia caused by hypertensive small vessel disease was given. Despite initiation of aspirin, improved blood pressure control, and a trial of cholinesterase inhibition, progressive cognitive decline ensued.

Comment. This case is consistent with vascular dementia due to diffuse subcortical cerebrovascular pathology, also called Binswanger disease. Despite the absence of symptomatic stroke, the silent brain infarcts and white matter hyperintensities appear to be sufficient to cause cognitive decline. The relatively young age at onset suggests that Alzheimer pathology is probably absent. However, the presence of comorbid Alzheimer pathology cannot be completely excluded as amyloid imaging studies in patients with subcortical ischemic dementia show that mixed dementia, with a contribution from Alzheimer pathology, is relatively common.

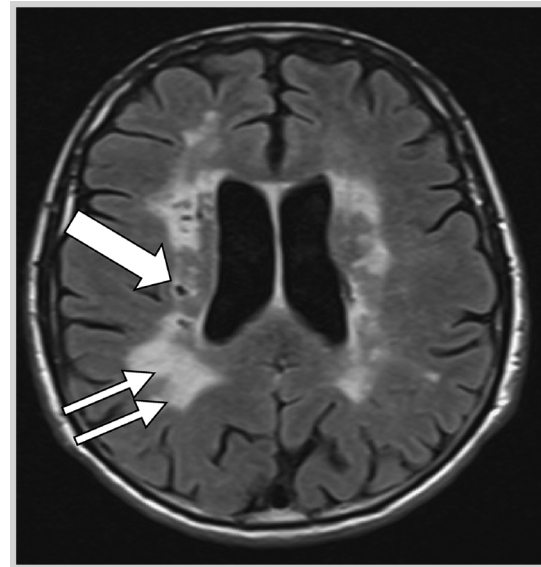


FIGURE 6-3

Axial fluid-attenuated inversion recovery (FLAIR) MRI of the patient in **Case 6-2** shows severe white matter hyperintensities (*double arrow*) with multiple lacunae of presumed vascular origin (*single arrow*).

may be more likely to affect cognition than small infarcts in other locations. Higher numbers of infarcts and higher volumes of white matter hyperintensities are associated with higher risk of cognitive impairment; however, exact thresholds are not well defined and likely vary based on the location of the lesions. To support a diagnosis of vascular cognitive impairment, the AHA/ASA recommends that “diffuse, subcortical cerebrovascular disease pathology” should be present,⁴ while the Vas-Cog Society recommends that at least three supratentorial brain infarcts or “extensive and confluent” white matter hyperintensities should be present.⁵ However, these recommendations, while useful aids to

clinical judgment, have not been studied for their validity in clinical practice.

Promising new MRI techniques not yet ready for clinical use may, in the future, allow better discrimination of clinically relevant from less clinically relevant cerebrovascular lesions by interrogating their impact on brain network function. Subcortical infarction and ischemic white matter demyelination are presumed to cause cognitive impairment by disconnecting brain networks subserving cognition. Recent MRI techniques have demonstrated that white matter hyperintensities of presumed vascular origin are associated with reduced structural brain connectivity measured using diffusion-tensor imaging,²² and that subcortical

KEY POINTS

- Microinfarcts are a substrate for vascular cognitive impairment, but are only visible at autopsy because they are too small to see on MRI.
- Although patients with vascular cognitive impairment often exhibit impairments in executive function and processing speed, other cognitive domains may also be affected.
- Motor signs that may accompany vascular cognitive impairment include frontal gait disorder, lower body parkinsonism, apathy, depression, urinary incontinence, spasticity, hyperreflexia, and frontal release signs.

infarction is associated with remote cortical atrophy in connected areas.²³

While neuroimaging remains the most useful diagnostic test to link the presence and severity of cerebrovascular disease with the presence of vascular cognitive impairment, the clinician must keep in mind that neuroimaging does not have perfect sensitivity for all clinically relevant cerebrovascular lesions. Specifically, neuroimaging is unable to detect microinfarcts, which are infarcts as small as 0.2 mm in diameter that are visible at autopsy in approximately one-quarter of all deceased elderly but in up to half of all deceased elderly patients with dementia.²⁴ These infarcts fall below the limit of spatial resolution of clinical MRI. About half the time they occur in the absence of gross infarcts, such that neuroimaging may falsely suggest the absence of infarction.

When the patient's neuropsychological profile matches the location and severity of cerebrovascular disease, the case for clinically relevant cerebrovascular disease is strengthened. Most commonly, vascular cognitive impairment is associated with relatively greater impairments in executive function and processing speed than in episodic memory for a given level of overall disability.⁴ By contrast, early AD is most often associated with episodic memory impairment.²⁵ However, it is important to recognize that some degree of memory impairment is very common in vascular cognitive impairment as well.⁴ Furthermore, the clinician should be aware that there can be great variety in the spatial distribution and severity of cerebrovascular disease, which determines the neuropsychological profile. Therefore, there is no one uniform pattern of neuropsychological impairment in all patients with vascular cognitive impairment. For this reason, a diagnosis of vascular cognitive

impairment should not be made based on neuropsychological profile alone, but should be supported by other evidence from clinical history, neurologic examination, and neuroimaging that is consistent with vascular cognitive impairment. Nonetheless, neuropsychological testing may be very helpful when uncertainty exists regarding the clinical significance of cerebrovascular disease by identifying whether the neuropsychological profile is more or less consistent with the identified cerebrovascular lesions in that individual patient. Some vascular cognitive impairment diagnostic criteria require specific supportive clinical features, such as executive dysfunction, to be present to diagnose nonstroke vascular cognitive impairment,^{5,7} while others do not.^{1,4}

The clinician's case for clinically relevant cerebrovascular disease can be further strengthened if other motor manifestations of cerebral infarction or hemorrhage are identified based on history and clinical examination. Noncognitive manifestations of cerebrovascular disease include frontal gait disorder, lower-body parkinsonism, apathy, depression, urinary incontinence, spasticity, hyperreflexia, and frontal release signs.⁵ Additionally, behavioral disturbances such as apathy, depression, and emotional incontinence are frequent as well.⁵ The presence of these signs, in the absence of competing nonvascular causes, suggests symptomatic cerebrovascular disease with the implication that the cerebrovascular disease could also be affecting cognition.

Nonatherosclerotic and Nonarteriolosclerotic Causes of Vascular Cognitive Impairment

The next sections review two important causes of vascular cognitive

impairment unrelated to the conventional vascular factors that cause atherosclerosis and arteriolosclerosis: cerebral amyloid angiopathy and monogenic inherited cerebrovascular diseases.

Cerebral amyloid angiopathy. Cerebral amyloid angiopathy is caused by vascular β -amyloid deposition in the cerebral cortex and leptomeninges, leading to fragility of the vessel wall with rupture and bleeding in some patients.²⁶ Cerebral amyloid angiopathy is the second most common cause of intracerebral hemorrhage in elderly patients, after hypertensive vasculopathy. Because vascular amyloid tends to spare the arteries supplying the internal part of the brain, cerebral amyloid angiopathy-related hemorrhages predominately occur in the superficial, lobar portions of the cortex and underlying white matter, or in the adjacent subarachnoid space, with sparing of the basal ganglia and the brainstem. This lobar pattern of hemorrhages and superficial siderosis forms

the basis for clinical diagnosis during life (Table 6-4).²⁷

The diagnosis of cerebral amyloid angiopathy is greatly aided by the use of MRI with hemorrhage-sensitive sequences such as susceptibility-weighted imaging (SWI), which allows demonstration of microbleeds caused by cerebral amyloid angiopathy. Positron emission tomography (PET) amyloid tracers bind to vascular amyloid as well as senile plaques, and, therefore, cannot be used to distinguish between vascular and parenchymal amyloid deposits.

Cerebral amyloid angiopathy and AD exist on a spectrum. Most patients with AD have some amount of vascular amyloid, although compared to patients with cerebral amyloid angiopathy-related hemorrhage, the deposits are more likely to be around capillaries than within the walls of arterioles. Patients with AD rarely have hemorrhagic strokes, although the frequency of microbleeds is higher than in non-AD controls. Conversely,

TABLE 6-4 Modified Boston Criteria for Cerebral Amyloid Angiopathy–Related Hemorrhage^a

Probable Cerebral Amyloid Angiopathy

1. Age ≥ 55
2. Either multiple hemorrhages restricted to lobar, cortical, or cortico-subcortical regions (cerebellar hemorrhage allowed) *OR* single lobar, cortical, or cortico-subcortical hemorrhage and focal or disseminated superficial siderosis
3. Absence of other cause of hemorrhage or superficial siderosis

Possible Cerebral Amyloid Angiopathy

1. Age ≥ 55
2. Either single lobar, cortical, or cortico-subcortical hemorrhage *OR* focal or disseminated superficial siderosis
3. Absence of other cause of hemorrhage or superficial siderosis

^a Modified with permission from Linn J, et al, *Neurology*.²⁷ www.neurology.org/content/74/17/1346.short. © 2010 American Academy of Neurology.

KEY POINTS

- Cerebral amyloid angiopathy is an important cause of vascular cognitive impairment, with effects that are independent of the degree of accompanying Alzheimer disease pathology.
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is the most common inherited monogenic cause of vascular cognitive impairment.
- Vascular cognitive impairment is the second most common cause of cognitive impairment and frequently coexists with other neurodegenerative pathologies as mixed dementia.

most patients with cerebral amyloid angiopathy do not have AD dementia.

Community-based autopsy studies show that cerebral amyloid angiopathy is associated with cognitive impairment and risk for dementia, even after accounting for the association between cerebral amyloid angiopathy and AD (Case 6-3).²⁸ Controlling for the degree of coexisting Alzheimer pathology, cerebral amyloid angiopathy was associated with worse episodic memory and perceptual speed.²⁹ These cognitive impairments could be caused by cerebral amyloid angiopathy-related microinfarction, ischemic white matter demyelination, impaired vascular reactivity, or the cumulative effects of hemorrhages.³⁰ There are no disease-modifying treatments for cerebral amyloid angiopathy.

Monogenic inherited causes of vascular cognitive impairment. The presence of confluent white matter hyperintensities or multiple lacunae in excess of that expected by age and not explained by conventional vascular risk factors should prompt consideration of an inherited cause of vascular cognitive impairment, particularly when a family history is present.³¹ The inherited cause of vascular cognitive impairment, which is the most commonly encountered and best studied, may be cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). CADASIL is an autosomal dominant disease caused by mutations in the *NOTCH3* gene. Affected patients develop migraine, lacunar stroke, and then vascular cognitive impairment due to the cumulative effects of multiple lacunar infarcts and extensive white matter hyperintensities. There are no disease-modifying treatments. Other inherited diseases that can

cause vascular cognitive impairment include cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (a CADASIL-like disease caused by mutations in *HTRA1*) and mutations in the *COL4A1* gene.³¹

PREVALENCE, NEUROPATHOLOGY, AND RELATIONSHIP TO OTHER NEURODEGENERATIVE DISEASES

Both clinical and autopsy data show that vascular cognitive impairment is the second most common cause of later life dementia, after AD. Specialty-clinic-based studies show that vascular cognitive impairment is the diagnosis in about 10% of patients, while mixed dementia with a vascular component, often in combination with AD, is the diagnosis in a similar or even greater proportion of cases.³² Epidemiologic studies are generally consistent with the clinic-based studies in showing that vascular dementia is the second most common cause of dementia.³³ However, exact numbers on incidence and prevalence are difficult to establish because the different vascular dementia criteria appear to vary in their sensitivity and specificity, inhibiting cross-cohort comparisons.

Autopsy-based neuropathology studies of prevalence have a number of advantages over clinic-based studies. The autopsy allows quantitative or semiquantitative measurement of cerebrovascular lesions difficult to identify on in vivo imaging, such as microinfarction, and allows quantitative assessment of comorbid pathologies such as neurofibrillary tangles, amyloid plaques, and Lewy bodies. Ideally, neuropathology studies would be nested within community representative samples and have a high degree of participation in the autopsy arm to avoid the referral and

Case 6-3

A 73-year-old man was seen for forgetfulness and apathy that had been present for approximately 2 years. Activities of daily living were essentially preserved, with the exception of occasional minor errors such as purchasing incorrect items at the grocery store. The patient's Montreal Cognitive Assessment (MoCA) score was 24 out of 30. Scores on the Trail Making B test and a test of verbal recall were one standard deviation below the mean compared to normative values. Brain MRI showed six microbleeds on the gradient recalled echo (GRE) sequence, all in lobar locations (**Figure 6-4A**), and severe white matter hyperintensities on the fluid-attenuated inversion recovery (FLAIR) sequence (**Figure 6-4B**). Fluorodeoxyglucose positron emission tomography (FDG-PET) scan showed patchy hypometabolism, including in brain regions with microbleeds. However, metabolism in the posterior cingulate gyrus, a region typically affected by Alzheimer disease, was preserved, suggesting that Alzheimer disease was probably not the cause of the cognitive impairment. A diagnosis of probable vascular mild cognitive impairment was given, with cerebral amyloid angiopathy as the most likely vascular cause. Over the next 2 years, the patient progressed to mild dementia, with an essentially unchanged FDG-PET scan. Two years after the initial presentation, the patient had a right parietal intracerebral hemorrhage (**Figure 6-4C**), typical of cerebral amyloid angiopathy.

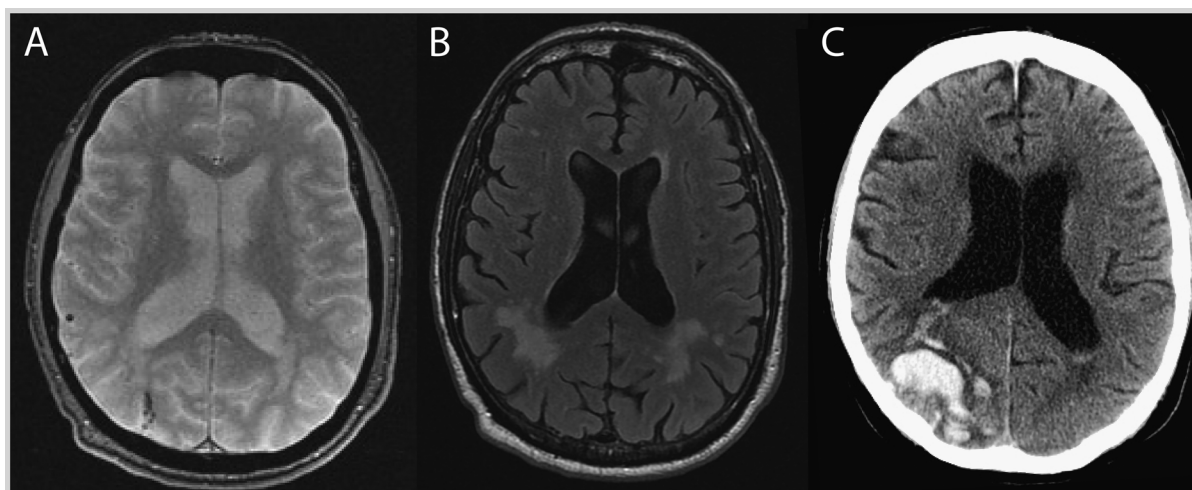


FIGURE 6-4

Axial MRI of the patient in **Case 6-3** shows six microbleeds on the gradient recalled echo (GRE) sequence, all in lobar locations (**A**), and severe white matter hyperintensities on the fluid-attenuated inversion recovery (FLAIR) sequence (**B**). Two years after initial presentation, the patient had a right parietal intracerebral hemorrhage (**C**), typical of cerebral amyloid angiopathy.

Comment. Probable cerebral amyloid angiopathy was diagnosed in this case on the basis of the Boston criteria (**Table 6-4**), which indicate that cerebral amyloid angiopathy is highly probable in patients with a lobar intracerebral hemorrhage and MRI evidence of one or more microbleeds restricted to lobar locations. Patients with multiple lobar-only microbleeds, without hemorrhagic stroke, are also likely to have cerebral amyloid angiopathy, although the Boston criteria have not been validated in this setting. Neuropathology studies show that more severe cerebral amyloid angiopathy is a predictor of cognitive impairment, controlling for the degree of accompanying Alzheimer pathology.

KEY POINTS

- Vascular cognitive impairment accounts for up to one-third of dementia risk.
- Patient and caregiver support to maintain quality of life and prolong community living are important aspects of vascular cognitive impairment management.

selection bias that may affect clinic-based studies.

Cerebrovascular lesions commonly measured at autopsy include infarcts, hemorrhages, arteriolosclerosis, and atherosclerosis. Microinfarcts, which may be the most clinically relevant vascular neuropathologic lesion, can be identified on histology but are usually not visible grossly or on *in vivo* MRI.²⁴ Conversely, it is important to recognize that some lesions readily visible on MRI, such as microbleeds, may be hard to find at autopsy and that MRI white matter hyperintensities, which have such a dramatic appearance on MRI, are difficult to visualize at autopsy without special stains and, therefore, can be overlooked.

Vascular pathology is extremely common at time of death, both in persons with and without dementia, being present in roughly 80% of brains overall.³⁴ By comprehensively measuring both vascular as well as comorbid neurodegenerative pathologies it is possible to estimate, in an unbiased and objective manner, the relationship between vascular pathologies and risk for dementia in community-based studies, while simultaneously controlling for other pathologies. Using this approach, autopsy studies consistently show that vascular pathology, mostly consisting of manifestations of cerebral small vessel disease such as small infarcts, independently predicts the risk of dementia even when accounting for Alzheimer and Lewy body pathology. These data suggest that vascular pathology accounts for roughly one-quarter to one-third of dementia risk.^{35,36}

The frequent co-occurrence of Alzheimer and vascular pathology with deleterious effects on cognition has raised scientific interest in whether there are deeper, fundamental inter-

actions between these most common pathologies of dementia. This interest has been heightened by recent observations that sporadic AD is associated with a failure of soluble amyloid- β (A β) clearance³⁷ and that soluble A β can exit the brain through vascular and perivascular clearance pathways.³⁸ However, autopsy studies generally show that the burden of cerebrovascular and Alzheimer pathology are independent of one another and that effects on the odds of dementia are additive, not multiplicative.³⁹ Thus, interactions between cerebrovascular and Alzheimer pathology seem to be in their combined effects on brain cellular and network function, and not because one disease directly causes the other; however, note that this observation does not exclude a role for variance in (non-diseased) vascular clearance of A β in the pathogenesis of AD.

MANAGEMENT OF VASCULAR COGNITIVE IMPAIRMENT

Management of vascular cognitive impairment may be categorized as patient and caregiver support, cognitive rehabilitation for poststroke vascular cognitive impairment, consideration of cognitive enhancing medications, and treatment and secondary prevention of the causative cerebrovascular process. Recommendations for the management of vascular cognitive impairment have been published by the AHA/ASA.⁴

Personal and caregiver support should follow general principles of management for patients with MCI or dementia and should include assessments of driving safety, safety in the home, financial and medical advanced planning, management of neuropsychiatric complications, and palliative care, as appropriate for the individual patient.⁴⁰

For patients with poststroke vascular cognitive impairment, cognitive rehabilitation may speed or improve recovery. Many patients with poststroke vascular cognitive impairment will experience improvements in cognition, or even resolution of cognitive deficits, during the stroke recovery process. Cognitive rehabilitation may include training for compensatory strategies or cognitive skills training.⁴¹

Randomized controlled trials of cholinesterase inhibitors show that they have a modest benefit in patients with vascular dementia, including in mixed vascular and AD dementia.⁴ The AHA/ASA and Canadian Best Practice Recommendations for Stroke Care recommend consideration of cholinesterase inhibitor therapy with intermediate-level evidence.^{4,41} The 2012 Canadian Consensus Conference on the Diagnosis and Treatment of Dementia recommends that cholinesterase inhibitor therapy should be considered in patients with AD with concomitant cerebrovascular disease, with intermediate-level evidence, but that there is insufficient evidence to recommend cholinesterase inhibitor therapy for patients with pure vascular dementia.⁴² Donepezil and galantamine are the best-studied cholinesterase inhibitors.⁴ The benefits of memantine are not well established.⁴ This author frequently uses acetylcholinesterase inhibitors in patients with progressive probable or possible vascular dementia, particularly when a contribution from comorbid AD cannot be excluded.

Perhaps the most important part of management of vascular cognitive impairment is the identification of the causative cerebrovascular processes and initiation of secondary prevention strategies to prevent their progression or recurrence. A list of causes of vascular cognitive impairment is shown in

Table 6-2. Many vascular diseases can be prevented or their progression can be slowed by existing therapies proven effective by randomized controlled trials. With adequate control of vascular risk factors, it may be possible to reduce the rate of progression of vascular cognitive impairment or even arrest any progression, as long as comorbid neurodegenerative pathologies are not also present and symptomatic. For patients with poststroke vascular cognitive impairment, stroke recurrence is a strong risk factor for cognitive worsening or onset of new dementia.

For patients with ischemic stroke, diagnosis of the causes and management of risk factors should be done according to ischemic stroke secondary prevention guidelines from the AHA/ASA.⁴³ For patients with intracerebral hemorrhage, diagnosis and management of risk factors should be done according to intracerebral hemorrhage guidelines.⁴⁴ Hypertension is the strongest risk factor for stroke overall and for each main stroke type individually, and therefore warrants careful attention to achieve adequate blood pressure control.

The management of patients with nonstroke vascular cognitive impairment, which is predominantly caused by cerebral small vessel disease, is less certain and lacks evidence from randomized trials. The most common cause of cerebral small vessel disease is arteriolosclerosis due to aging and vascular risk factors such as hypertension and diabetes mellitus. However, cerebral amyloid angiopathy is an important alternative cause in a minority of patients.⁴⁵ This author suggests that patients with arteriosclerotic cerebral small vessel disease should have measurement of blood pressure, an ECG to assess for atrial fibrillation,

KEY POINTS

- Acetylcholinesterase inhibitors have a modest beneficial effect in vascular cognitive impairment.
- The most important component of vascular cognitive impairment management is identifying and treating the underlying cerebrovascular processes that lead to brain injury.
- Patients with vascular cognitive impairment with stroke should be treated according to secondary prevention guidelines for stroke.

KEY POINT

- Careful control of vascular risk factors may be an important component of dementia prevention.

measurement of serum lipid profile, and measurement of either fasting blood glucose or glycosylated hemoglobin A_{1c} to assess for diabetes mellitus. More intensive investigations for proximal sources of embolism, such as echocardiography, prolonged cardiac rhythm monitoring for atrial fibrillation, and noninvasive carotid imaging for carotid-territory infarcts, should be considered in patients with infarcts that could be of embolic origin, such as cortical infarcts, but may not be necessary in patients with only small subcortical infarcts likely caused by intrinsic small vessel disease.

There are no proven therapies for prevention of cognitive decline in patients with cerebral small vessel disease.⁴⁵ Secondary prevention should focus on addressing the vascular risk factors identified in the diagnostic workup. It is reasonable to start aspirin in patients with silent brain infarcts, and this treatment may also be considered in patients with extensive, confluent white matter hyperintensities. When considering indications for statin therapy, it is not proven whether cerebral small vessel disease should be considered an atherosclerotic disease equivalent; therefore, the use of statins may be considered on a case-by-case basis in individual patients, particularly when there is hypercholesterolemia. White matter hyperintensity progression has been evaluated as a secondary end point in several randomized controlled trials. Progression is probably slowed by good blood pressure control⁴⁶ but was not slowed by intensive glucose management (to glycosylated hemoglobin A_{1c} level of less than 6.0%),⁴⁷ with mixed results for two trials of statin therapy.⁴⁸ A single trial of homocysteine-lowering vitamin therapy showed less MRI white matter hyperintensity progression in the treatment

arm, but only in patients with severe hyperintensities at baseline.⁴⁹ A limitation of all of these trials is that the sample sizes were not large enough to link slowing of white matter hyperintensity progression with reduction in clinical end points such as cognitive decline or stroke.

PREVENTION OF VASCULAR COGNITIVE IMPAIRMENT

Improved population control of vascular risk factors is one of the most promising approaches to dementia prevention. Stroke and cardiovascular mortality has been declining for several decades, probably partly related to better control of vascular risk factors as well as better acute management. There is emerging evidence that the age-standardized incidence of dementia is declining, but the degree to which this declining incidence can be attributed to better vascular risk factor control is unknown.⁵⁰ The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study randomly assigned participants to a vascular risk factor control regimen as part of a multidomain approach to dementia prevention and found that the multidomain intervention, which also included diet, exercise, and cognitive training, prevented decline in cognitive test scores.⁵¹

CONCLUSION

Vascular cognitive impairment is the second most common cause of dementia and is a frequent contributor to mixed dementia. All patients with cognitive impairment should be assessed for contributing vascular causes. The diagnostic approach should be based on identifying cognitive impairment, identifying vascular disease, including clinically hard-to-recognize cerebral

small vessel disease on neuroimaging, and then using clinical judgment to determine whether the two are related. Vascular cognitive impairment should be classified into poststroke and non-stroke forms. The most important aspect of vascular cognitive impairment management is to diagnose the causes and risk factors for the underlying cerebrovascular diseases and then initiate secondary prevention targeted against those diseases.

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