The term “vascular dementia” is often used as if it refers to only one condition, and research is often done on the same assumption. However, there are many etiologies responsible for cerebrovascular lesions, producing an array of clinical manifestations and psychological deficits. Lumping these conditions together may not be appropriate under all circumstances, but current practice does not recognize this. An integral part of a diagnosis of vascular dementia should be a statement concerning etiology, since this will inform treatment decisions.

Despite the recognition of both Alzheimer’s disease and a form of vascular dementia (Binswanger disease) at the end of the 19th century, for the greater part of the 20th century dementia was routinely attributed to arteriosclerosis and consequent chronic cerebral ischemia. This view changed with the increasing recognition of Alzheimer’s disease and the demonstration that infarcts, rather than chronic ischemia, were the basis of what came to be called “multi-infarct dementia.” The term “vascular dementia” subsequently replaced multi-infarct dementia since it was recognized that there were many etiologies apart from multiple infarcts (e.g., single infarcts, hypotension, leukoaraiosis, incomplete infarction, hemorrhage).

However, by the end of the 20th century, the increasingly recognized Alzheimer’s disease overshadowed vascular dementia.

Because Alzheimer’s disease was thought to be the major cause of dementia, its criteria became those applied to all dementia. Alzheimer’s was separated from vascular dementia using clinical features thought to reflect vascular risk factors, vascular events and the manifestations of systemic and cerebral vascular disease. These elements are typically codified using the ischemic score (see Table 1). The basis of the definition has resulted in the criteria for vascular dementia emphasizing memory loss and usually the progression and irreversibility of the cognitive decline, none of which is necessarily the case. A complete paradigm shift is required to develop new criteria and alternative screening tools that focus on the cognitive domains most affected in vascular disease.

In addition, dementia is defined as the level of cognitive impairment at which normal daily functions are impaired; this will identify only late cases, underestimating the prevalence of cognitive impairment due to vascular disease and depriving early cases the benefit of early preventative treatment. This critical early stage has been termed “vascular cognitive impairment.” Its importance lies in the fact that vascular disease is...
Vascular Dementia:

How to Solve the Puzzle of Cognitive Loss

This multifaceted diagnosis is overdue for a reappraisal. Here’s a look at how its definition, and its role in clinical practice, is evolving.

the largest single identifiable risk factor for dementia apart from age and the only one that is currently treatable.

Over the past decade, there has been another major change: the increasing recognition of mixed dementia, where vascular dementia co-exists with other causes, particularly Alzheimer’s disease. These are now known to be common. Eighty percent of the elderly have evidence of cerebrovascular disease, and mixed VaD/AD may account for up to one-half of all dementia cases. Furthermore, the interaction between the vascular component and other components more than doubles the rate of progression when compared to pure Alzheimer’s disease alone.

Clinical Manifestations

Two similar sets of vascular dementia identification criteria have been proposed, but neither has met universal acceptance or been validated. Furthermore, they are difficult to apply consistently and produce different results.

The NINDS-AIREN criteria define probable vascular dementia as decline in memory and two or more cognitive domains severe enough to interfere with activities of daily living. Evidence of cerebrovascular disease on both clinical examination and neuroimaging is required, as is evidence of a relationship between the stroke and cognitive decline. The latter can be provided by two of the following: (a) onset of dementia within three months after a recognized stroke, (b) abrupt deterioration in cognition and (c) stepwise deterioration.

Abnormalities on neuroimaging support the diagnosis of vascular dementia only if they fulfill criteria regarding site and size. These criteria include large-vessel strokes in the following sites: bilateral anterior cerebral, posterior cerebral, association areas or carotid watershed (superior frontal, parietal); small-vessel disease in the basal ganglia and frontal white matter; extensive periventricular white matter lesions; or bilateral thalamic lesions. The criteria for severity specify that leukencephalopathy must involve at least 25 percent of the total white matter.

A diagnosis of possible vascular dementia is made (a) if there is clinical evidence of cerebrovascular disease but no neuroimaging data; (b) in the absence of a clear temporal relationship between dementia and stroke; or (c) in those cases with a subtle onset and variable course. Hemorrhagic lesions are permitted. Definite vascular dementia is diagnosed provided probable dementia exists, accompanied by histopathological evi-
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dence of cerebrovascular disease and no histopathological evidence of other possible causes of the cognitive loss. Vascular dementia is excluded in cases with disturbed consciousness, psychosis, severe aphasia, major sensorimotor deficits or other brain diseases such as Alzheimer’s disease that could themselves account for the deficit. Mixed dementia is not recognized, but the coexistence of Alzheimer’s is termed “Alzheimer’s disease with cerebrovascular disease.”

The California criteria are not fundamentally different, but they do differ in details. Hemorrhagic and anoxic lesions are not included. The number and type of cognitive defects are deliberately not specified, but the loss should be sufficient to interfere with the conduct of the patient’s customary affairs of life and should not be confined to a single narrow category. Two or more ischemic strokes (at least one of which is outside the cerebellum) or one stroke with a clear temporal relationship to the onset of dementia are required. Risk factors and some clinical features are included as supportive features, but how these are to be operationalized is not stated. The ischemic scale, while not intended to be the sole instrument used in the separation of Alzheimer’s disease from vascular dementia, is accurate in this role. It cannot, however, separate vascular dementia from mixed dementia.

As there is no generally accepted definition of vascular dementia, its manifestations are not agreed on and data from studies using current criteria for vascular dementia cannot be used to describe it or to validate the criteria. For example, an analysis of case series meeting current criteria for vascular dementia should reveal memory loss in all cases. This may be taken as showing memory loss to be universal in vascular dementia. This is so only because it is defined that way. If the criteria are wrong, so is case identification. A better source of information may be to look at the cognitive changes seen in stroke in general without any selection by artificial, and probably incorrect, criteria. Such series are few but increasing in number.

The studies to date identify a variety of patterns of cognitive loss; the differing patterns often depending on case selection. The predominating theme, however, is of a primary subcortical dementia with early impairment of frontal lobe function. Memory is involved but is often not pre-eminent. Although the cases reported in these studies may not all meet the currently proposed criteria for vascular dementia, the patterns of cognitive loss reported may be more appropriate to the development of a definition of vascular dementia than the currently proposed criteria that depend on memory loss.

The presence of “patchy” or unequal cognitive deficits is a requirement for a diagnosis of vascular dementia in ICD-10, but this pattern of cognitive loss is to be expected only in true multi-infarct dementia, where there are few (two or three) cortical infarcts. In vascular dementia in general, the extent to which the cognitive deficit is patchy is not different from Alzheimer’s disease; however, the domains affected are different.

Atrophy on MRI has sometimes been taken to support degenerative or mixed dementia rather than vascular dementia. Now, though, clear evidence shows that atrophy, particularly central atrophy, is a common feature in vascular dementia and also in association with vascular risk factors, transient ischemic attacks, and leukoaraiosis. The presence of atrophy should, therefore, not weigh against a diagnosis of vascular dementia.

Pathogenesis and Pathophysiology

The processes that lead to vascular dementia may begin before infarction has occurred. Risk factors, particularly hypertension, without clear vascular events are associated with both a relative increase in the volume of the lateral ventricles, suggesting central atrophy and cognitive decline. In addition, there is the aforementioned association between atrophy and vascular cognitive impairment. Atrophy may, therefore, be associated with both vascular disease and degenerative dementia, rather than just being a hallmark of degenerative dementia as previously supposed, and is similar in these various processes.

Although early reports on the effects of leukoaraiosis on cognition were mixed, there is now clear evidence that leukoaraiosis is associated with both cognitive impairment and focal signs in otherwise normal individuals. Even in early vascular cognitive impairment, there is a weak association between leukoaraiosis and cognitive loss. Indeed, leukoaraiosis may be the earliest correlate of cognitive symptoms. Functional imaging (diffusion tensor MRI) shows abnormalities of diffusivity in normal-appearing white matter in patients with leukoaraiosis, and diffusivity correlates better with cognition than with simple lesion load.

Leukoaraiosis is etiologically associated with hypertension and a history of stroke, suggesting a vascular cause. It is not
associated with carotid disease. Episodic hypotension occurring through transient dysrhythmias, nocturnal hypotension or carotid sinus hypersensitivity superimposed on a background of diminished vascular reserve may be one group of etiological mechanisms for both leukoaraiosis and incomplete infarction. Data concerning hypotension as a risk factor for vascular dementia remain contradictory.\(^{26-27}\)

The term leukoaraiosis encompasses a range of pathologies. The term was originally used in the context of CT white matter changes, but it is also used to refer to white matter changes on MRI. However, it encompasses a wide range of structural changes ranging from increased water content without functional loss through to axon or myelin loss and these all appear similar or identical on MRI. This is a reason for the relatively poor correlation between leukoaraiosis and cognition.

Infarct volume is also a factor, but because of the importance of location, it is not the sole determinant. There has been debate over the minimum volume of infarction needed to produce dementia, but this is a matter of limited significance given the importance of infarct location. It is unlikely that there exists a precise volume of infarction that can reliably predict vascular dementia other than at meaninglessly large volumes. Within any one location, the correlation between infarct volume and cognition improves as would be expected as the effect of location is minimized. 

Infarcts located at sites such as the thalamus can be crucial. However, the most important locations outside these strategic locations are a matter of dispute, partly because of the application of variable methods to differing populations. Evidence has variously favored bilateral, left-sided, thalamic, anterior cerebral artery territory and frontal lesions. Various patterns important in producing dementia have also been suggested: thalamic plus cortical, cortical and white matter, and dominant hemisphere. Some work favors a special role for lacunar and other deep lesions over cortical lesions, but other work does not. These contradictory findings will not be resolved until uniform criteria for patient selection and cognitive assessment have been developed.

Lesions interact synergistically, and the study of neural nets in cognition provides some clues as to why this may be. In a neural net, loss of one set of connections can initially be circumvented by the use of other circuits, which may be slower and less efficient but may improve with use (learning). Thus, initial ischemic damage, particularly in the white matter, may not leave detectable deficits. However, the scope for recovery after further lesions decreases, and lesions late in the disease process may cause disproportionate damage because their loss removes both their normal functions and the additional functions acquired as part of the recovery process after earlier events. Therefore, neural nets provide scope for recovery after lesions, but as the number of lesions increases, this scope decreases, the consequences of each successive lesion thus increasing.

Neural nets also give clues to the probable order of cognitive decline produced by multiple lesions that would initially affect the systems most dependent on complex neural nets. This partly explains why the frontal involvement is one of the most prominent and why there may be frontal lobe deficits even when there is no damage within recognized frontal lobe connections. Memory, which also depends on an extensive neural net, may also be affected relatively early but not most prominently. However, this would not hold true in cases where the basis of the vascular dementia was not multiple small lesions, and the pattern of cognitive loss would be much more closely linked to the precise site of the lesion.

Even so, patients with right-sided lesions exhibit impairment in verbal IQ and patients with left-sided lesions exhibit impairment in performance IQ. This clearly shows the importance of generalized cognitive processing, presumably based on neural nets, as opposed to the more traditional localization of function. Intuitively, sequential deficits closely spaced in time should leave a more severe deficit than the same lesions spaced far enough apart for complete recovery between lesions, but this hypothesis remains untested.
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Prevention

There is little consistent information regarding risk factors. It is not clear whether the risk factors for vascular dementia are the same as those for stroke, as VaD may be more often due to small vessel disease than stroke in general. Although hypertension is certainly a powerful risk factor for vascular dementia, whether it is a disproportionate risk factor remains unproven. Recent data from the PROGRESS and Systolic Hypertension in Europe studies do, however, show that reduction of blood pressure protects against dementia in general.26-29

A number of large, long-term studies have reported that modifying vascular risk factors reduces incident cognitive impairment and dementia. In updated results from the Syst-Eur study,30 a reduction of 7mm Hg in systolic and 3.2mm Hg in diastolic blood pressure over 3.9 years cut in half incident dementia. The absolute figures are a little less impressive at three cases per 100 patient years. A variety of other risk factors have been identified (with varying degrees of clinical impact) in various studies, including hypertension, heart disease, diabetes, hyperlipidemia, smoking, carotid bruits, age, male sex, education, race, prior stroke, ECG changes, hematocrit, history of myocardial infarction, carotid atherosclerosis, low-density lipoprotein cholesterol, isolated systolic hypertension and proteinuria. There is clearly much overlap with stroke. Evidence that modification of many of these risk factors protects against vascular dementia is lacking, but it is reasonable to do so on first principles.

There is now clear evidence that atrial fibrillation is a risk factor.31-32 This association is curious given the usual association of atrial fibrillation with large infarcts. The suggested mechanism is by silent infarction; however, dysrhythmias producing hypotension and incomplete infarction cannot be ruled out. The truth of the matter, as yet unknown, is important as it would affect the most appropriate management. Orthostatic hypotension may also play a role, but nocturnal dipping of blood pressure may not.

Vascular risk factors in middle age, particularly hypertension, may predict cognitive loss in later life—even when the risk factors themselves have resolved—and may also accelerate the appearance of Alzheimer’s disease in later life.33-34 Putative nonvascular risk factors include high alcohol consumption, psychological stress in early life, use of aspirin (presumably a vascular marker), low education, blue collar occupation, occupational exposure to a pesticides, herbicides, liquid plastic or rubber, and premorbid personalities that make subjects more liable to stress or psychosomatic reactions. Most of these require confirmation and quantification.

There are now increasing data on drugs as preventive agents. Interestingly, evidence that the statins protect against cognitive loss is relatively weak. The PROSPER study of 6,000 individuals aged 70 to 82 years was unable to demonstrate any benefit on stroke, cognition or activities of daily living, but the study did show a benefit on myocardial infarction and TIA.35 Given the established benefits of the statins in preventing adverse vascular events, the discrepancy between these and antihypertensive therapy requires some explanation. The discrepancy may lie in the fact that subcortical vascular dementia is the single most common form of vascular dementia and that hypertension is, by a considerable margin, the most powerful treatable risk factor. Cholesterol has little association with small-vessel disease and the plaque-stabilizing antioxidant, and other properties attributed to the statins may not be relevant to lipohyalinosis or to small-vessel disease. Taking these observations together, it is readily possible to see why different treatments may have differing effects.

Aspirin has been proposed on the basis of a pilot study done without placebo.36 Other nonsteroidal analgesics do not protect against vascular dementia.37 The PROGRESS study did not confirm a “window” effect, but it did provide evidence for the efficacy of treating hypertension in the secondary prevention of dementia after stroke or transient ischemic attack.38 Primary prevention by control of blood pressure seems to make little

What Causes Vascular Dementia?

Subcortical vascular dementia is becoming increasingly recognized as the most common single variant of vascular dementia, accounting for perhaps 40 percent of cases. Infarcts contribute to most cases of vascular dementia, but multiple smaller infarcts and small vessel disease are more often a substrate of vascular dementia than single major infarcts.

In vascular dementia, cognitive decline may begin with the presence of risk factors alone, especially hypertension and presumably the damage at this stage is at a microscopic level. Leukoaraiosis, hemorrhages, amyloid angiopathy, vasculitides, angioendotheliosis and incomplete infarction are less common etiological factors. Incomplete infarction comprises zones of partial neuronal or axonal loss with demyelination, increased perivascular spaces, reactive astrogliosis, gliosis, and sparse macrophages. Silent infarcts also contribute to cognitive decline. Ischemic hippocampal sclerosis may account for a significant proportion of cases. Environmental factors, rather than hereditary factors, seem to play a major role in vascular dementia as distinct from Alzheimer’s disease.
difference, but importantly, the Honolulu-Asia aging study has reported that treatment of midlife hypertension can reduce the risk of subsequent dementia.\textsuperscript{19,28}

Although a subject of much debate, the consumption of antioxidant vitamins in midlife may also protect against vascular dementia.\textsuperscript{40}

**Differential Diagnosis**

The principal differential diagnoses are Alzheimer's disease and depression following stroke. In 90 percent of cases where multiple infarcts are responsible, there is also a history of stroke or of transient ischemic attacks. However, in cases where subcortical ischemic change is the vascular mechanism, a history of stroke may be absent in up to 40 percent, and focal signs are also less common.\textsuperscript{41} The use of the ischemic scale score (see Table 1) has 89 percent sensitivity and specificity. However, distinguishing mixed dementia and either vascular dementia or Alzheimer's disease remains difficult, with poor specificity. The use of CT to identify infarcts increases diagnostic accuracy.

Compounding the difficulty of identifying vascular dementia is its common coexistence with Alzheimer's disease and the important effect of cerebrovascular disease to hasten the clinical manifestation of Alzheimer's in what are, in effect, mixed cases even though there may be no specific history of stroke and the vascular disease may amount to only microinfarcts. Furthermore, many previous studies concerning the diagnosis of Alzheimer's have dismissed small volumes of ischemic damage. In view of the interaction between cerebrovascular disease and Alzheimer's disease, this now seems highly inappropriate, and about one-quarter of cases of clinically diagnosed “pure” Alzheimer's disease will have some vascular component.\textsuperscript{4}

Of at least equal importance to the identification of VaD itself is identification of the cause of the vascular events, since the treatment and prognosis depend on the cause. The remainder of the differential diagnosis is that of dementia.

**Diagnostic Workup**

Dementia can be established by the clinical history and examination alone, including an assessment for depression. Imaging is required to confirm the occurrence of cerebrovascular disease and to exclude structural causes. Although MRI will better show leukoaraiosis and may be essential if certain conditions such as CADASIL are suspected, CT is sufficient in routine clinical practice. The presence of white matter lesions on CT (but not on MRI) may help to distinguish vascular dementia from Alzheimer's disease. Cortical sulcal atrophy and ventricular enlargement are more severe in patients with multiple infarcts and dementia than in those with multiple infarcts without dementia, but there is no evidence to suggest that this is sufficiently discriminating to be a useful part of the evaluation.

The vascular component of the investigations should be directed by clinical suspicion. Not all investigations are routinely required. However, a complete blood count, erythrocyte sedimentation rate, glucose, and ECG should be done. Where appropriate, carotid duplex Doppler, chest X-ray, echocardiography, Holter monitoring, thrombophilia screen, lipid profile, lupus anticoagulant, anticardiolipin antibodies, and autoantibody screen are justifiable. A glycosylated hemoglobin may detect unsuspected diabetes. Cerebral angiography is indicated if carotid surgery is considered or to demonstrate beading of the smaller cerebral vessels if a cerebral vasculitis is suspected, but it is not a routine investigation and may in any case miss an active vasculitis. CSF examination may be required if an infectious or inflammatory etiology is suspected as, in rare cases, may be dural or brain biopsy.

**Infarcts located at sites such as the thalamus can be crucial.**

**However, the most important locations outside these strategic locations are a matter of dispute.**

Evidence has variously favored bilateral, left-sided, thalamic, anterior cerebral artery territory and frontal lesions.

**Prognosis and Complications**

The prognosis of vascular dementia varies considerably according to the criteria used to make the diagnosis.\textsuperscript{42} Multi-infarct dementia shortens life expectancy to about 50 percent of normal at four years from initial evaluation.\textsuperscript{43-44} Females, people with higher education, and those who perform well on some neuropsychological tests do better. In the elderly, three-year mortality may reach two-thirds, almost three times that of controls.\textsuperscript{45} In one study, the six-year survival was only 11.9 percent, about one-quarter of that expected,\textsuperscript{46} although many of these patients were elderly and severely demented at entry.

About a third die from complications of the dementia itself, one-third from cerebrovascular disease, eight percent from other cardiovascular disease, and the rest from miscellaneous causes, including malignancy.\textsuperscript{46} Overall, the effect of vascular
dementia on mortality is similar to, or mildly worse than, that of Alzheimer’s disease. However, some allowance has to be made for the criteria used to define vascular dementia in each case, and in the worst case, the mortality is almost twice that of the best.42

In one study, cognitive impairment short of dementia (i.e., vascular cognitive impairment) increased the likelihood of subsequent dementia from eight to 42 percent after nine years of follow-up.47 In the Canadian Study of Health and Aging, approximately half of subjects were dead and half institutionalized after five years. However, in 16 percent there was no cognitive decline and even some cases of improvement, reflecting the diversity of potential outcomes in this condition.48

Management
The treatment of vascular dementia is that of the underlying cause. Care must be taken to identify and treat depression, which is common both in association with dementia and after stroke. If there is any doubt, a course of treatment with antidepressant medication is usually justifiable.

Begin treatment of hypertension cautiously. Chronically hypertensive patients shift the autoregulatory range for cerebral blood flow to accommodate higher perfusion pressures. Even with treatment, this will not fully return to normal. They are, thus, susceptible to hypotension, which is a suspected mechanism for vascular dementia. Measures of general application to dementia of all kinds are also appropriate, including referral to community services and local support groups, consideration of caregiver stress, and legal and ethical issues such as driving, competency, and advance directives.

A few drug trials have been completed. There is some evidence for nimodipine in subcortical vascular dementia.49-50 Memantine may help in dementia in general (including mixed disease), may reduce the burden on caregivers,51 and offers some benefit in vascular dementia alone without major side effects.52-54 Propentofylline may improve cognitive function on formal testing but does not seem to affect activities of daily living.55-58 Some evidence exists for vincamine,59 vinpocetine,60 pentoxifylline61-62 and posatirelin.63 As yet, though, there is no convincing evidence for any single drug, and none of these can be recommended.

The acetylcholinesterase inhibitors may be more helpful. Data from three trials have now been published, encompassing a variety of probable and possible vascular dementia cases as well as mixed dementia. These show statistically significant, but modest, benefits for galanthamine and donepezil over placebo in both cognition and activities of daily living.64-66 However, it is possible that these benefits are merely due to the drugs’ effect on coexistent Alzheimer’s disease67 or the effect may be non-specific. PN

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