

Clinical Forms of Vascular Dementia

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1. INTRODUCTION

The presence of vascular dementia (VaD) is largely unrecognized and untreated in the elderly (1,2). The typical history is that of an elderly parent or grandparent who fails to regain the previous level of function and independence after a stroke. More often, in the absence of the heralding stroke symptoms, the family notices that the patient has become depressed and apathetic, exhibits personality changes, experiences social inhibition, and has slowing mental capacity and sluggish motor activities with the inability to solve simple daily problems. Walking becomes deliberate, insecure, with a shuffling character and short steps; patients become unsteady on their feet and may take frequent falls. Often, the patient also suffers from urinary urgency, stress incontinence, and nocturia. Patients are no longer able to perform simple activities of daily living (ADLs), such as using the bathroom, showering, getting dressed, cooking, shopping, participating in rehabilitation activities and exercise routines, or performing more complex tasks, such as using the telephone or balancing a checkbook. Frequently, these changes occur after a surgical procedure, such as abdominal surgery, knee or hip replacement, or coronary artery bypass graft (CABG).

The primary care physician is often surprised to find normal or minimally impaired results in the Mini-Mental State Examination (3) (MMSE) or the Cambridge cognitive capacity scale (CAMCOG) (4), which is the cognitive portion of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX). The physician may conclude that the patient is depressed, or “deconditioned,” after hospitalization, and these symptoms are dismissed as part of a slow convalescence. Nonetheless, the overall net result is dementia, i.e., the loss of cognitive function and the dependency on others for ADLs. The MMSE and the CAMCOG test memory and other posterior cortical functions that are specifically designed to detect Alzheimer’s disease (AD), which is a cortical dementia. Therefore, most screening tests for dementia are completely insensitive to alterations of executive function, a cognitive domain localized in prefrontal-subcortical circuits selectively impaired in subcortical forms of VaD (5). This chapter reviews these and other clinical differences between AD and VaD.

2. DEFINITIONS

Vascular dementia: Vascular dementia (VaD) is the loss of cognitive functions to a degree that interferes with ADLs, resulting from ischemic or hemorrhagic cerebrovascular disease (CVD) or from cardiovascular or circulatory disturbances that injure brain regions that are important for memory, cognition, and behavior (1). VaD is the second most common form of dementia after AD, accounting for approximately 20% of dementia cases worldwide (6). Globally, VaD is more common in men, especially before age 75—in contrast with AD that predominates in women—and is

more prevalent in populations that are affected by cerebral small-vessel disease, such as Asians, Blacks, and Hispanics. In keeping with the predictions of increasing burden of stroke and heart disease in the near future (7), VaD will probably become the most common cause of senile dementia, both by itself and as a contributor to other degenerative dementias (8).

Vascular cognitive impairment: Vascular cognitive impairment (VCI) is a recently coined term to signify any degree of cognitive loss caused by CVD, including vascular dementia (9,10). However, by analogy with mild cognitive impairment (MCI) resulting from AD (11), the term VCI is better reserved for patients with risk factors for CVD and some degree of cognitive loss short of dementia. Intrinsic to the VCI concept is the hope that appropriate prevention and treatment of CVD can prevent VaD development. Although this is an appealing undertaking, there have been difficulties in providing a strict definition of VCI and operational diagnostic criteria. The concept of VCI suffers from the same problems once criticized in VaD; i.e., the notion is too wide and too vague for a precise operative definition. Furthermore, as demonstrated in the Canadian Study on Health and Aging (12,13), some patients with a diagnosis of VCI no dementia (VCI-ND) improved with time, indicating that progression from VCI to VaD may not always be a unidirectional pathway. There is growing evidence that preventive measures to decrease the vascular burden on the brain may also decrease VaD, as well as AD (14). This may be achieved by controlling hypertension and cardiac disease, lowering lipids with the use of statins, by decreasing homocysteine, with smoking cessation, and with a Mediterranean diet, among other factors. Moreover, it is hoped that by preventing CVD, the onset of symptomatic AD can be delayed, thereby decreasing the overall burden of dementia.

Mixed dementia: The boundaries between VaD and AD recently have become indistinct. The belief that CVD may lead to cognitive decline and dementia in the elderly has been around since 1672, when Thomas Willis first described cases of postapoplectic dementia. Less well recognized is that *silent* strokes and incomplete white matter ischemia—documented by modern brain imaging—are also strongly associated with cognitive loss, behavioral changes, and VaD. During most of the past two centuries, it was widely held that atherosclerotic dementia was the sole cause of senile dementia. It was only in the 1980s that AD was declared the most common form of dementia in the elderly. However, most elderly patients with dementia who are autopsied will have amyloid plaques and neurofibrillary tangles, the typical brain lesions of AD, localized in the hippocampal regions (Braak Stages I–III), coexisting with cerebrovascular lesions, such as large and small strokes, hemorrhages, arteriolosclerosis, lacunes, microinfarcts, and ischemic leukoencephalopathy. CVD is required to “amplify” the clinical expression of AD pathology beyond the stage of amnesic MCI (Braak Stage III). This explains why almost 20% of cases pathologically defined by Consortium to Establish a Registry for Alzheimer Disease (CERAD) criteria as AD do not have clinical dementia. Conversely, more than half of the octogenarians without dementia meet CERAD criteria for pathologically confirmed AD (15). On the other hand, Hénon and colleagues (16,17), have also shown that in patients with bona fide postapoplectic VaD, preexisting amnesic deficits occurred in 16% of cases, suggesting that the underlying AD had not progressed beyond Stage III, which is clearly insufficient to produce clinical dementia. Evidence from the Nun Study (18) also concluded that lacunes increase more than 20 times the risk of clinical expression of dementia at early Braak stages that are insufficient to produce dementia. Moreover, in pathologically confirmed cases of “mixed” dementia (AD+CVD, AD+VaD), there is a significant *inverse* relationship between the severity of CVD and Braak stage (19–22). In all these patients, VaD is the defining cause of the dementia. In addition, population-based studies have shown that silent lacunes are extremely common in the elderly. Longstreth et al. (23) showed the presence of one or more silent lacunes in approximately one-fourth of the 3,660 participants in the Cardiovascular Health Study (CHS) aged 65 and older that underwent cerebral magnetic resonance imaging (MRI). Recently, in the Rotterdam cohort, Vermeer et al. (24) demonstrated that the presence of lacunes, particularly in the thalamus, more than doubled the risk of dementia (hazard ratio = 2.26, 95% CI, 1.09–4.70). Small-vessel disease may be the most common mechanism to convert from MCI into AD in persons over the age of 70 yr (8).

Table 1
Risk Factors for Vascular Dementia

<ul style="list-style-type: none">• Advanced age• Isolated systolic hypertension in the elderly• Cigarette smoking• Hyperhomocysteinemia• Congestive heart failure• Other cardiac arrhythmias• Recurrent stroke• Obstructive sleep apnea• Coronary artery bypass graft surgery	<ul style="list-style-type: none">• Long-term, untreated arterial hypertension• Diabetes mellitus• Hyperlipidemia• Hyperfibrinogenemia• Atrial fibrillation• Complicated stroke• Orthostatic hypotension• Major surgery in the elderly
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The weight of the evidence validates the hypothesis that CVD is the most important cause of dementia in the elderly, both by itself and as a catalyst for the conversion of low-grade AD to dementia. As customarily done in neuroepidemiological studies (25), patients with AD+CVD should be included among the VaDs and not in the AD category. Moreover, to this group of patients we must add the thousands of cases with cognitive loss and VaD resulting from cerebral hypoperfusion complicating cardiac and circulatory diseases. The evidence presented notwithstanding, it should be emphasized that AD is not primarily a vascular disease as postulated by de la Torre (26).

3. CLINICAL FORMS OF DEMENTIA

3.1. When to Suspect VaD

Typically, patients with VaD are not found in memory disorder clinics, because memory loss is a less prominent manifestation of this syndrome. This must be considered when extrapolating figures of dementia prevalence from hospital- or office-based data. This also explains the alleged rarity of VaD in neuropathologically examined specimens from brain banks of AD clinics (27). Primary care settings (family physicians and geriatricians) are the main referral source of patients with VaD. These cases occur among patients affected by coronary artery disease (CAD), stroke, diabetes mellitus, transient ischemic attacks (TIAs), arterial hypertension, cigarette smoking, increased homocysteine, and hyperfibrinogenemia. VaD affects elderly persons with systolic hypertension, congestive heart failure (CHF), atrial fibrillation and other cardiac arrhythmias, orthostatic hypotension, or obstructive sleep apnea (*see* Table 1).

Poststroke VaD also occurs among patients recovering from recurrent strokes in rehabilitation services and stroke clinics. Likewise, VaD secondary to cerebral hypoperfusion is seen in cardiac rehabilitation patients after myocardial infarction (MI) (28) or among patients convalescing from major surgery, particular hip fracture repair (29). Approximately 26% of patients discharged from the hospital after treatment for CHF have significant cognitive decline (30). Patients with severe cognitive dysfunction usually have worse left ventricular dysfunction and systolic blood pressure levels below 130 mmHg. Cognitive decline resulting from cerebral embolism and hypoperfusion is also frequently found in patients' post-CABG surgery (31–33). Patients with VaD and severe behavioral manifestations (apathy, agitation, and uninhibited behavior) are usually seen by geriatric psychiatrists, who have coined the terms *vascular depression* and *depression-executive dysfunction syndrome of late life* for this clinical syndrome (34,35).

3.2. Cortical and Subcortical Dementias

Clinicians divide the dementia syndrome into two main types, *cortical* and *subcortical*, according to the clinical features and the pattern of neuropsychological impairment. The prototypical cortical

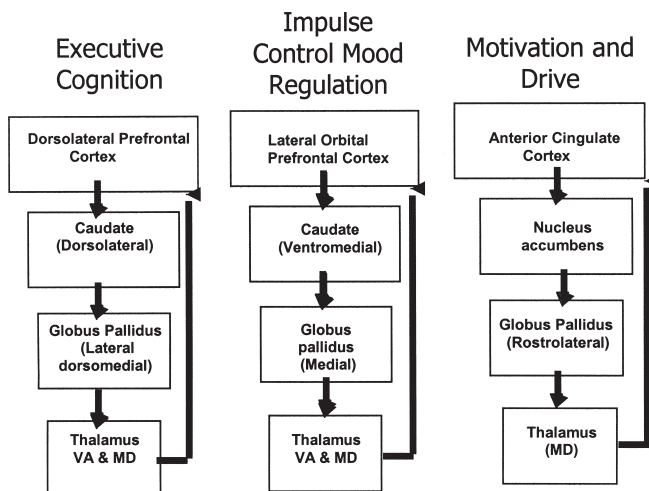


Fig. 1. Frontal-subcortical-thalamic circuits: the prefrontal cortex is connected to the striatum and thalamus in parallel but separate circuits that help regulate behavior; there is topographic mapping of caudate and thalamus. A typical feature of these prefrontal cortico-subcortical circuits is that an injury anywhere in a circuit can produce a major deficit and small subcortical lesions can mimic large cortical lesions.

dementia is AD that manifests preponderantly with early and severe memory disturbances, aphasia, agnosia, and apraxia resulting from lesions involving posterior cortical association regions. In sharp contrast, VaD manifestations, a typical subcortical dementia, include slowing of cognition and motor function owing to executive control (5), along with prominent alterations of gait (36), speech, affect, and mood. The manifestations mentioned result from the interruption by ischemic lesions of frontal cortico-subcortical circuits (see Fig. 1) for executive control of memory, language, mood, construction skills, motivation, and socially responsive behaviors (37–42).

Unfortunately, there is a dearth of bedside executive function tests (42). Commonly used tests include Luria's kinetic melody (43), the Clock Drawing Test and Executive Function (CLOX) (44), and the trail test part B (45), as well as verbal fluency tasks and similarities tests in the Modified Mini-Mental State (3MS) (46) and the Cognitive Abilities Screening Instrument (CASI) (47). Clinical experience indicates that frontal system involvement is common in VaD and is a constant component of subcortical VaD.

4. CLINICAL FORMS OF VAD

VaD is a complex neuropathological entity resulting from several causal vascular lesions with numerous clinical manifestations (see Table 2). However, according to Román (48), the clinical syndromes of VaD may be divided simply into two main groups, *acute* and *subacute*, according to the temporal profile of clinical presentation.

4.1. Acute-Onset (Poststroke) VaD

Acute-onset VaD (also called poststroke, postictal, or postapoplectic VaD) includes patients with new-onset dementia after a clinically eloquent acute cerebrovascular event. The causal stroke is either a single strategic stroke resulting from occlusion (or rupture) of a large-size vessel or a symptomatic subcortical lacunar stroke caused by occlusive small-vessel disease. The older term *multistroke dementia* (MID) is sometimes used when VaD develops after recurrent large-vessel strokes. Table 3

Table 2
Clinical and Pathological Forms of Vascular Dementia

Large-vessel dementia	
Mechanisms	<ul style="list-style-type: none"> • Artery-to-artery embolism • Thrombosis/occlusion of extracranial or intracranial cerebral arteries • Cardiogenic embolism
Multi-infarct dementia	<ul style="list-style-type: none"> • Multiple large complete infarcts, cortico-subcortical in location, usually with perifocal incomplete infarction involving the white matter
Strategic infarct dementia	<ul style="list-style-type: none"> • Single brain infarct in functionally critical areas of the brain (angular gyrus, thalamus, basal forebrain, posterior cerebral artery, and anterior cerebral artery territories)
Small-vessel dementia	
Mechanisms	<ul style="list-style-type: none"> • Endothelial dysfunction appears to be the final common pathway of hypertension, diabetes, smoking, aging, and other risk factors for small-vessel brain disease
Subcortical ischemic VaD	<ul style="list-style-type: none"> • Binswanger's disease • CADASIL • Lacunar dementia or lacunar state (<i>état lacunaire</i>) • Multiple lacunes with extensive perifocal incomplete infarction
Cortical-subcortical	<ul style="list-style-type: none"> • Hypertensive and arteriolosclerotic angiopathy • Cerebral amyloid angiopathies • Other hereditary forms • Collagen-vascular disease with dementia • Moyamoya • Cerebral sinus/venous thrombosis
Ischemic-hypoperfusive dementia	
Border-zone infarction	<ul style="list-style-type: none"> • Restricted injury resulting from due to selective vulnerability
Ischemic leukoencephalopathy	<ul style="list-style-type: none"> • Incomplete white-matter infarction
Hemorrhagic dementia	
	<ul style="list-style-type: none"> • Traumatic subdural hematoma • Subarachnoid hemorrhage • Cerebral hemorrhage • Hematological factors

Abbr: VaD, vascular dementia; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

summarizes the main risk factors for poststroke MID. It has been estimated that approximately 20% of patients older than 65 yr who suffer an ischemic stroke develop poststroke VaD (49–51).

Clinically, large-vessel forms of poststroke VaD may resemble the cortical dementias in the accumulation of stroke-related cortical cognitive deficits, such as agnosia, apraxia, alexia, aphasia, often without motor deficit (52,53). The latter cases result from relatively unusual (strategic) ischemic strokes that involve single branches of the middle cerebral artery (MCA), the anterior (ACA), or the posterior cerebral artery (PCA) and their branches (52,53). For example, strokes of the left posterior parietal branch of the MCA with ischemia of association areas in the posterior portions of the superior and inferior parietal lobules, including the supramarginal gyrus, usually produce cortical sensory loss with astereognosia, agraphesthesia, and proprioceptive loss, Wernicke's aphasia, and Gerstmann's syndrome with right-left disorientation, finger agnosia, acalculia, and agraphia (53).

Table 3
Main Risk Factors for Poststroke Vascular Dementia

1. Age	Older age
2. Education	Lower educational level
3. Personal factors	Lower income, current smokers
4. Genetic factors	Family history of dementia
5. Stroke type	Recurrent strokes
6. Stroke location	Left-sided lesions, “strategic strokes” (i.e., posterior association areas, such as gyrus angularis; posterior cerebral artery territories, including paramedian thalamic artery territory, inferomedial temporal lobes, and hippocampus; watershed or border-zone infarcts mainly involving superior frontal and parietal regions; bilateral anterior cerebral artery territories, anterior choroidal artery strokes, and basal forebrain lesions; and frontal white matter lesions). Inferior capsular genu stroke producing diaschisis of frontal lobes and cerebellum.
7. Stroke volume	Lesions larger than 50–100 mL of tissue destruction, large perilesional incomplete ischemic areas involving white matter, larger periventricular white matter ischemic lesions.
8. Stroke complications	Hypoxic and ischemic complications of acute stroke (i.e., seizures, cardiac arrhythmias, aspiration pneumonia, and hypotension).
9. Stroke manifestations	Dysphagia, gait limitations, and urinary impairment.

However, amnesia is not present and, despite, the multiple deficits, with time many of these patients recover their independence in ADLs and no longer fulfill the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria for dementia (54). This contrasts the memory loss and the usual deterioration of AD with time. When stroke patients recover and return to functional capacity or are left with isolated poststroke cognitive deficits, they are usually classified under the heading VCI.

Nonetheless, there are VaD cases with amnesia as a prominent feature resulting from interruption by ischemic injury of portions of the circuit comprising the hippocampus, fornix, mamillary body, mammillothalamic tract, anterior thalamus (55,56). Memory loss may also occur with mediobasal forebrain damage (57). Sometimes the amnesic manifestations of the lesions mentioned may be confused clinically with AD. A brief summary of the main features of acute-onset VaD associated with large-vessel stroke follows.

4.1.1. Posterior Cerebral Artery

Brandt and colleagues (58), found that approximately 25% of patients with infarctions in the PCA territory present with amnesia as a result of damage to the hippocampus, isthmus, entorhinal and perirhinal cortex, and parahippocampal gyrus. Lesions that are more limited may occur with territorial infarctions of the anterior or posterior choroidal arteries. Unilateral lesions cause material-specific memory loss (verbal amnesia with left-sided lesions and loss of visuospatial memory and memory for locations with lesions on the right side), whereas bilateral damage gives rise to global amnesia (53,57). In some patients with mesial temporal lobe lesions (hippocampus and its projections), episodic anterograde amnesia—similar to that of AD—may be observed (58). These patients are unable to encode and consolidate new verbal material, facts; events, short stories, names, and concepts their but working memory and procedural memory are intact; confabulations are uncommon (53,57,59).

Visual signs in more than 80% of patients usually accompany the memory deficits in PCA strokes. These include homonymous hemianopsia, color agnosia, and visual agnosia. Left-sided lesions may have transcortical sensory aphasia, pure alexia, or alexia without agraphia. Spatial disorientation

may be prominent with right-sided lesions. Anton's syndrome of cortical blindness with anosognosia occurs with bilateral occipital lesions. Bilateral parietooccipital infarctions above the calcarine fissure may result in Balint's syndrome with simultagnosia, optic ataxia, and ocular apraxia; prosopagnosia occurs with bilateral occipital ischemia below the calcarine fissure.

4.1.2. Basal Forebrain Infarction

Lesions of the mesial temporal lobe and thalamus causing memory and other cognitive deficits may interrupt cholinergic projections to these regions (60). However, in humans, a single study of 12 patients with MID failed to find changes in the nucleus basalis of Meynert (nbM) (61). Direct ischemic injury of the cholinergic nuclei in the basal forebrain has been documented in patients with subarachnoid hemorrhage from ruptured aneurysms of the anterior communicating artery (AComA), usually after surgical repair (62,63). The damage results from aneurysmal bleeding and from sacrifice of perforating branches of the AComA or proximal ACA at the time of surgery. After surgical repair of an aneurysm of the AComA, Phillips et al. (64) found severe anterograde amnesia for verbal or visuospatial material, along with severe apathy, lack of initiative and spontaneity, and executive dysfunction. Postmortem neuropathological lesions were found in midline basal areas, rostral to the anterior commissure and lamina terminalis, destroying the medial septal nuclei (Ch1), the vertical portion (Ch2) of the nucleus of the diagonal band of Broca (ndbB), the nucleus accumbens, and adjacent areas. Damage to the cholinergic neurons in the septal nucleus and ndbB determine the persistence of the amnesia (63,64).

From the clinical viewpoint, most patients with AD have severe anterograde episodic amnesia with extremely poor recall of verbal material. Although a similar type of amnesia may result from localized strokes, in general, most subjects with VaD perform better on story recall and word list learning (California and the Rey verbal learning tests); also, in contrast with AD patients, they are usually able to respond to cues and have superior free recall and relatively minor deficits of verbal long-term memory (65). Patients with VaD retain speech and calculation longer than those with AD.

4.1.3. Thalamic VaD

This peculiar form of VaD, described originally by Castaigne et al. (66,67), occurs after paramedian thalamic ischemic strokes. Lesions involve the anterior (polar) thalamus (68,69) in territories irrigated by the polar thalamic artery, which is a branch of the posterior communicating artery, or the medial and central thalamus involving the dorsomedial nucleus (DMn) and the mamillothalamic tract (70). The latter two structures are irrigated by the paramedian thalamic artery which is a branch of the basilar-PCA. For Van der Werf et al. (70), the critical lesion in the production of thalamic amnesia is the damage of the mamillothalamic tract, which projects into the anterior nuclei of the thalamus and then to the cingulate cortex.

All patients have a depressed level of consciousness that gradually improves within days to weeks, revealing impairments in attention, motivation, initiative, executive functions, and memory, as well as dramatic verbal and motor slowness and apathy (71). Gaze abnormalities are common and include vertical gaze paresis, medial rectus paresis, and absent convergence. Dysarthria and mild hemiparesis may be present when the lesions extend to the subthalamic and midbrain tegmentum in the superior paramedian mesencephalic artery territory, which may arise adjacent to or from a common trunk with the paramedian thalamic artery.

Left thalamic lesions are accompanied by memory deficits more often than right-sided lesions; verbal and, occasionally, visual memory loss are present with left-sided lesions and visual amnesia with right-sided lesions. Global amnesia occurs with bilateral lesions or in those with simultaneous damage to the mamillothalamic tract and the inferior thalamic peduncle. These patients have severe anterograde episodic amnesia plus retrograde amnesia; i.e., both the encoding of new memories and retrieval of new and old memories are affected, but motor learning and implicit memory are intact (53). The severe attentional and motivational deficits play a role in the amnesia (68,71).

4.1.4. *Inferior Genu Stroke*

A clinical syndrome, which is closely related to thalamic VaD, was described by Tatemichi and colleagues (72,73) in patients with a lacunar infarction in the inferior genu of the internal capsule. This characteristic—albeit relatively uncommon—syndrome is manifested by a sudden change in cognitive function, often associated with fluctuating attention, confusion, abulia, striking psychomotor retardation, inattention, executive dysfunction, and other features of frontal lobe dysfunction but with mild focal findings, such as hemiparesis or dysarthria. Memory loss was present in all cases: left-sided infarcts had severe verbal memory loss and right-sided infarcts caused visuospatial memory loss (74,75).

Lacunar strokes of the inferior genu of the internal capsule result from involvement of anterior perforators arising from the internal carotid artery (ICA) or from the ACA. These arteries are commonly affected by hypertension and other forms of small-vessel disease and could be an unrecognized cause of cognitive deficits. For instance, Ghika et al. (76) found neuropsychological deficits in up to 34% of patients with lacunes in the territory of deep perforators of the ICA system identified by brain computed tomography (CT).

Furthermore, a lacunar stroke involving the inferior genu of the internal capsule causes ipsilateral blood flow reduction to the inferior and medial frontal cortex (72,73,77) and to the ipsilateral temporal lobe and contralateral cerebellar hemisphere (77), by a mechanism of diaschisis. These lesions in the genu of the inferior capsule may sever corticothalamic and thalamocortical fibers in the thalamic peduncles, which detach from the internal capsule to enter the thalamus at its rostral and caudal poles and along its dorsal surface. The *anterior thalamic peduncle* connects the DMn with the cingulate gyrus, prefrontal, and orbitofrontal cortex. The *inferior thalamic peduncle* connects the thalamus with orbitofrontal, insular, and temporal cortex, as well as with the amygdala, via the ansa peduncularis and the amygdalofugal pathway. The last two named also contain cholinergic fibers from the nbM (Ch4) and may have an effect in reducing blood flow. Thus, lacunar infarctions in the region of the inferior genu cause both frontal behavioral effects and memory loss associated with functional deactivation of the ipsilateral frontal and temporal cortex.

Finally, there are also rare amnesic syndromes with subcortical lesions interrupting frontal networks, separate from the traditional Papez circuit or the Delay-Brion memory system (56).

4.1.5. *Caudate Strokes*

The loss of memory observed with caudate strokes is characterized by recall difficulties even with cues but with normal recognition (53). These features, along with the typical abulia (78,79), probably result from interruption of frontal connections. Frontal and temporal hypoperfusion in these cases may conceivably result from interruption of cholinergic projections.

4.2. *Subacute (Subcortical) VaD*

Subacute VaD follows a slowly progressive course seen mainly in patients with nonocclusive small-vessel disease affecting periventricular white matter (Binswanger's disease), usually accompanied by clinically asymptomatic lacunes; a stepwise worsening may occur when small-vessel occlusion leads to recurrent lacunar strokes (2). This pattern of clinical onset and progression is the same one observed in patients with CADASIL (80–82). Most subcortical VaD cases have a subacute presentation and result from the combination of nonocclusive small-vessel disease and lacunes (2). The temporal profile of presentation of these forms of VaD is typically subacute with a chronic course marked by fluctuations and slowly progressive worsening that resembles that of AD. Patients present clinically with frontal lobe deficits, executive dysfunction, slow information processing, impaired memory, inattention, depressive mood changes, motor involvement, parkinsonian features, urinary disturbances, and pseudobulbar palsy. Frontal executive functions control volition, planning, programming, and monitoring of complex goal-directed activities, such as cooking, shopping, and housework (2,5). Loss of executive function is a major component of cognitive disability and dementia

resulting from the loss of planning capacity, working memory, attention and concentration, stimuli discrimination, abstraction, conceptual flexibility, and self-control (39–42). Patients with executive dysfunction are often capable of performing individual steps of a complex problem but are unable to provide a correct strategy to solve it.

As mentioned, this is one of the most common forms of VaD and results from small-vessel disease with lacunes and white matter lesions that damage structures (caudate nucleus, globus pallidus, thalamus, and connecting fibers) of the prefrontal-subcortical circuits (37–40). The main forms of subacute subcortical VaD are lacunar state (*état lacunaire*), Binswanger's disease, CADASIL, and some forms of cerebral amyloid angiopathy. Diagnostic criteria for subcortical VaD have been recently proposed (83).

4.2.1. Lacunar State (*État Lacunaire*)

This clinical syndrome of the elderly results from the presence of multiple brain lacunes. Occlusion of the arterial lumen of small arterioles, including deep thalamoperforating and long medullary arterioles, leads to lacunar strokes. Lacunes are small areas of ischemic necrosis and liquefaction less than 15 mm in diameter, typically located in the basal ganglia, internal capsule, thalamus, pons, corona radiata, and centrum semiovale, and usually seen in the chronic cavitated stage (84). White matter lacunes may overlap with nonconfluent focal areas of ischemic leukoencephalopathy. Lacunes must be distinguished from dilated perivascular spaces (*état criblé*). Microscopically, these cavities show no evidence of necrosis, macrophages, or tissue debris and have a small vessel within the lacuna. In addition to lacunes, ventricular dilatation and white matter lesions resulting from recurrent ischemia-hypoxia frequently coexist. Patients may have a history of repeated small strokes with transient motor deficits or minimal residuum or the subacute presentation of Binswanger's disease. Cognitive deficits in patients with subcortical lacunes correlate better with the extent of white matter lesions than with the number of lacunes.

As mentioned, approximately one-fourth of the 3660 participants in the CHS had one or more lacunes demonstrated by cranial MRI (23). The CHS is a population-based random sample of the elderly US population that includes African Americans age 65 and older. In most of these participants (89%), lacunes were clinically silent; however, gait problems and subtle cognitive impairments—not recognized as stroke—were found more often in those with silent lacunes than in subjects with normal MRI (23). Similar results, with frequencies of silent lacunes ranging from 11 to 24%, have been found in other population-based studies, as well as in patient cohorts of initial stroke.

4.2.2. Binswanger's Disease

In 1894, Binswanger described the presence of an ischemic periventricular leukoencephalopathy that typically spares the arcuate subcortical U fibers as the hallmark of this condition (85). Small-vessel disease and multiple lacunes often coexist in Binswanger's disease, and it has been postulated that this condition and the so-called "lacunar dementia" of patients with lacunar state may represent a single entity (86).

Their clinical manifestations are similar and consist of a cognitive and motor syndrome, with characteristics of subcortical dementia, including executive dysfunction, loss of verbal fluency, slowing of motor function with perseveration, impersistence, inattention, difficulties with set shifting, and abnormal Luria's kinetic melody tests. Memory loss is characterized by poor retrieval and intact recognition. Apathy, depression, and behavioral problems are common. Mild residual hemiparesis or other discrete focal findings are often found. There is a peculiar short-stepped gait (*marche à petits pas*), dysarthria, pseudobulbar palsy, and, in some cases, astasia-abasia. Extrapyramidal features, such as inexpressive facies, slowness of movement, axial rigidity, loss of postural reflexes, frequent falls, increased urinary frequency, and nocturia, are also common findings (85). The differential diagnosis is with the clinical triad of dementia, abnormal gait, and urinary incontinence typical of normal pressure hydrocephalus.

4.2.3. Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

One of the most important recent developments in the field of VaD has been the clinical and genetic description of CADASIL (80). Originally called familial Binswanger's disease, this condition offers a natural model for the study of subcortical-subacute forms of VaD, particularly Binswanger's disease. Numerous pedigrees have been described in Europe and North America.

CADASIL is an autosomal dominant disorder of cerebral small vessels mapped to chromosome 19q12 (81,82). Clinical manifestations include TIAs and strokes (80%), cognitive deficits and VaD (50%), migraine with focal deficits (40%), mood disorders (30%), and epilepsy (10%). Onset is usually in early adulthood (mean age 46 yr) in the absence of risk factors for VaD, culminating in dementia and death usually approximately 20 yr after symptom onset. The dementia is slow in onset, subcortical and frontal in type, accompanied by gait and urinary disturbances, and pseudobulbar palsy clinically identical to that of sporadic Binswanger's disease. MRI reveals a combination of small lacunar lesions and diffuse white matter abnormalities; these are often present in asymptomatic relatives. Also, cerebral blood flow reactivity to inhaled carbon dioxide is impaired.

The underlying vascular lesion is a unique nonamyloid nonatherosclerotic microangiopathy involving arterioles (100–400 μ in diameter) and capillaries, primarily in the brain but also in other organs. The diagnosis may be established by skin biopsy (87) confirmed by immunostaining with a *Notch3* monoclonal antibody (88).

The vessels show deposits of eosinophilic, PAS-positive material in the arterial media that on electron microscopy consists of granular osmiophilic deposits and accumulation of the ectodomain of the *Notch3* receptor in the basal lamina of degenerated smooth muscle cells (87). The brain lesions are ischemic infarcts, mainly lacunar strokes, localized in basal ganglia, thalamus, centrum ovale, and pons and associated with extensive, confluent areas of frontal ischemic leukoencephalopathy, particularly in periventricular regions.

4.2.4. Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy (CAA) is a heterogeneous group of disorders characterized by deposition of amyloid in the walls of leptomeningeal and cerebral cortical blood vessels, characterized clinically by recurrent or multiple lobar hemorrhages, cognitive deterioration, and ischemic strokes. MRI displays diffuse white matter abnormalities, along with ischemic or hemorrhagic focal brain lesions. On histology, the vessels show amyloid deposition, microaneurysms, and fibrinoid necrosis. There are several autosomal dominant forms of CAA with differences in their clinical, genetic, biochemical, and pathologic findings. A β , the major amyloid component in the Dutch-, Flemish-, and Iowa-type of familial CAA, is also the major amyloid component in sporadic CAA and in AD. However, at least in the Dutch-type, the severity of the dementia correlates better with the degree of vascular lesions than with the amount of amyloid deposition (89). Familial British dementia (FBD) with amyloid angiopathy is an autosomal dominant condition characterized by VaD, progressive spastic paraparesis, and cerebellar ataxia, with onset in the sixth decade (90). A point mutation in the BRI gene on chromosome 13 is the genetic abnormality. On brain MRI, Binswanger-type deep white-matter hyperintensities and lacunar infarcts are seen, but no intracerebral hemorrhages are seen. The corpus callosum is severely affected and atrophic. Plaques and tangles are present, but the amyloid subunit (ABri) found in FBD brains is entirely different and unrelated to other amyloid proteins. FBD combines neurodegeneration and dementia with systemic amyloid deposition (91,92).

5. DIAGNOSIS OF VAD

Although numerous diagnostic criteria for VaD have been proposed, the NINDS-AIREN criteria (54) (see Table 4) have been used in most controlled clinical trials and offer an operative approach to the basic elements needed to reach a diagnosis of VaD. These are: (1) *cognitive loss*, (2) *cerebrovas-*

Table 4
NINDS-AIREN Diagnostic Criteria for Vascular Dementia*

I. The criteria for the diagnosis of *probable* VaD include *all* of the following:

1. Dementia: Impairment of memory and two or more cognitive domains (including executive function), interfering with ADLs and not resulting from effects of stroke alone.
 Exclusion criteria: Alterations of consciousness, delirium, psychoses, severe aphasia or deficits precluding testing, systemic disorders, *Alzheimer's disease*, or other forms of dementia.
2. Cerebrovascular disease: Focal signs on neurological examination (hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, dysarthria) consistent with stroke (with or without history of stroke, *and* evidence of relevant CVD by brain CT or MRI including *multiple large-vessel infarcts* or a *single strategically placed infarct* (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as *multiple basal ganglia* and *white-matter lacunes* or *extensive periventricular white-matter lesions*, or combinations thereof.
 Exclusion criteria: Absence of cerebrovascular lesions on CT or MRI.
3. A relationship between the above two disorders: Manifested or inferred by the presence of one or more of the following:
 - a. onset of dementia within 3 mo after a recognized stroke,
 - b. abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

II. Clinical features *consistent* with the diagnosis of *probable* VaD include the following:

1. Early presence of gait disturbances (small step gait or *marche à petits pas*, or magnetic, apraxic-ataxic, or parkinsonian gait).
2. History of unsteadiness and frequent, unprovoked falls.
3. Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease.
4. Pseudobulbar palsy.
5. Personality and mood changes, abulia, depression, emotional incontinence, or other deficits, including psychomotor retardation and abnormal executive function.

III. Features that make the diagnosis of VaD uncertain or unlikely include:

1. Early onset of memory deficit and progressive worsening of memory and other cognitive functions, such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging.
2. Absence of focal neurological signs, other than cognitive disturbances.
3. Absence of CVD on CT or MRI.

Abbr: ACA, anterior cerebral artery; ADLs, activities of daily living; CT, computerized tomography; CVD, cerebrovascular disease; MRI, magnetic resonance imaging; PCA, posterior cerebral artery; VaD, vascular dementia.

From G. Román et al (56).

cular lesions demonstrated by brain imaging (CT, MRI), (3) a *temporal link* between stroke and cognitive loss, and (4) *exclusion of other causes of dementia*, such as AD. A temporal relationship, i.e., development of dementia within 3 mo after stroke, has proved to be more difficult to fulfill, particularly in patients with silent strokes.

The NINDS-AIREN criteria require objective proof of dementia, validated by neuropsychological tests. In practical terms, tests for subcortical dysfunction, including executive function testing, should be used (93). Demonstration of the presence of vascular lesions by brain imaging MRI or CT is needed. Lesions range from a single strategic lacunar stroke to multiple cortical-subcortical strokes to periventricular ischemia. Mungas et al. (94) determined by MRI that hippocampal atrophy, volume of cortical gray matter, and volume of white matter lesions—but not lacunes—were strong and

independent predictors of vascular cognitive impairment. The neuropathological substrate of the lesions mentioned in patients with VaD is widespread ischemia from microvascular disease, including ischemic hippocampal injury pathologically resembling mesial temporal lobe sclerosis (95,96). By definition, absence of vascular lesions by brain imaging excludes VaD.

5.1. Separating AD From VaD

A practical problem that frequently confronts the internist is the elderly patient with cognitive and behavioral decline, presenting with abnormal score in the MMSE and presence of vascular lesions on brain imaging. The *ischemic score* may provide elements for the diagnosis of VaD (97). A score of 7 or more is consistent with MID, a score of 4 or less with AD, and a score of 5 to 6 is suggestive of AD plus CVD. In a recent meta-analysis (98), the following features were found more often in VaD than in AD: stepwise deterioration, fluctuating course, history of hypertension, history of stroke, and focal neurological symptoms.

Careful interview of relatives and caregivers should provide elements for the diagnosis of prestroke dementia (16,17). In most instances, probable AD is a likely etiology for the progressive memory loss occurring before the ictus. The amnesic form of MCI is easily identifiable and carries a risk of conversion to clinically probable AD at a rate of 10 to 15% per year, compared with 1 to 2% per year in healthy age-matched control subjects (99). However, the frequency and severity of CVD in older patients with AD point to the possibility that vascular risk factors may predispose not only to VaD but also to the AD development (100). Population-based epidemiological data have shown that vascular risk factors, such as hypertension, carotid artery wall thickness, cholesterol, and peripheral vascular disease often occur in patients who develop AD (14). The vascular role of the apolipoprotein E ϵ 4 allele, which is a risk factor for AD, may explain, in part, this interaction. Early treatment and control of vascular risk factors are one of the most promising avenues for the prevention of dementia in the elderly.

6. CONCLUSIONS

In summary, the diagnosis of VaD is relatively straightforward in most patients who have significant vascular risk factors and acute development of cognitive deficits and dementia after a clinically eloquent stroke. The diagnosis of VaD should also be entertained when these manifestations occur in patients after a cardiovascular episode, such as MI or CHF, in elderly patients recovering from laborious surgical procedures, in particular hip- or knee-replacement, and more often after a CABG surgery.

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Vascular Dementia

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