Chapter 7
Vascular Cognitive Impairment and Vascular Dementia

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Clinical Pearls

- The clinical triad of urinary incontinence, gait disturbance, and cognitive decline—commonly associated with normal pressure hydrocephalus (NPH)—is more often due to cerebrovascular disease [1].
- Although no neuroimaging criteria have been developed to define a threshold of white matter involvement sufficient to cause VaD, several experts and clinical trials have used a threshold of 25% involvement (of total white matter) for defining VaD [2].
- There are no medications specifically approved for use in VaD, however, patients with VaD may benefit from a trial of a cholinesterase inhibitor and/or memantine. General principles of pharmacological management of VaD follow those of the pharmacological management of AD: slow titration to maximum doses, using only one cholinesterase inhibitor at a time, adding memantine to cholinesterase therapy in the moderate to severe stages of disease.

Introduction

Cerebrovascular disease is an important cause of cognitive dysfunction, second only to Alzheimer's disease (AD) as a cause of dementia in the elderly [3]. The construct of dementia due to cerebrovascular disease has evolved over time and a

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number of different terms have been used including Binswanger's disease, multi-infarct dementia, and post-stroke dementia. These terms were often inconsistently applied and focused solely on memory dysfunction. Presently, the preferred term is vascular cognitive impairment (VCI) because it captures the entire spectrum of cognitive impairment attributable to cerebrovascular disease and also acknowledges the impact that vascular lesions have on the expression of other neurodegenerative processes (mixed syndromes) [4]. In its mildest form, VCI affects a single cognitive domain and independent functioning is preserved. In its most severe form, multiple cognitive domains are impaired and patients are described as having vascular dementia (VaD). VaD is caused by a variety of pathologies, and can present clinically with multiple phenotypes. Current diagnostic criteria require the clinician to establish a clear relationship (temporal, severity, or cognitive pattern) between the presence of vascular disease and cognitive impairment. It is still unclear, however, whether identified vascular lesions are the sole cause of cognitive dysfunction, are contributing to the expression of other disease processes, or are present but not impacting cognitive function. More recently, multiple autopsy studies have also shown that microinfarcts, which are not readily by currently used 1.5 T and 3 T magnetic resonance imaging (MRI) and noted in 7 T MRI, are major risk factors for cognitive impairment.

Determining the threshold of cerebral tissue damage required to cause dementia has proven difficult and there are no established pathological criteria for VaD as there are for other neurodegenerative diseases. There is, however, strong evidence that the likelihood of cognitive dysfunction increases with both lesion volume and number [5]. This, along with prospective cohort studies showing that recurrent stroke is a major independent risk factor for dementia [6], suggests that the course and prognosis of VaD is strongly related to additional vascular injury. Because the risk factors for and secondary prevention of cerebrovascular disease are well established, interventions for VaD may have a greater clinical impact than for other neurodegenerative disorders. Accurate assessment and management of vascular risk factors are, thus, a priority in the treatment of VaD. Although there are no approved therapies to overcome cognitive impairment in VaD, several agents used for AD have demonstrated modest cognitive benefits. A trial of one of these agents as well as proper management of any neuropsychiatric symptoms that emerge during the disease course are important components of the symptomatic management of VaD.

Epidemiology

While studies vary greatly, many experts believe that cerebrovascular disease is responsible for 10–20% of all dementia cases [3, 4]. The estimated prevalence rate of VaD is between 1 and 4% of individuals over the age of 65 [7]. Like AD, VaD is strongly age related, with prevalence rates doubling every 5.3 years after age 65 [4]. In individuals over the age of 85, the prevalence of VaD approaches that of AD [8]. Mixed dementia syndromes including cerebrovascular disease co-occurring with AD, Lewy bodies, or frontotemporal pathology are increasingly recognized. 25–80% of elderly dementia patients show mixed pathologies on autopsy [9].

Risk Factors

A large body of evidence has demonstrated the significant relationship between stroke and dementia. In general, having a stroke doubles the risk of developing dementia [4]. Risk factors for dementia after stroke include increasing age, low education status, diabetes, atrial fibrillation, stroke location (particularly left hemisphere), the presence of multiple strokes, and temporal lobe atrophy (suggestive of concurrent AD pathology) [10]. In the absence of clinical stroke, advancing age and vascular risk factors are associated with an elevated risk of VaD [11]. Additional risk factors linked to VaD—physical inactivity, the metabolic syndrome, smoking, stroke—are also risk factors for AD and suggest a possible shared pathophysiology [12].

Clinical Manifestations

The clinical manifestations of VaD are diverse and may include a wide variety of cognitive, behavioral, and/or physical changes. Several factors influence clinical presentation including the location of injury, volume of tissue injured, pathology causing the injury (i.e. hemorrhagic vs. ischemic), presence of concurrent neurodegenerative diseases, and time between brain injury and clinical evaluation. Table 7.1 lists the main VaD subtypes. The cognitive changes in VaD can generally be divided into two patterns—one in which the clinical features are attributable to damage to the large vessels supplying the cerebral cortex (cortical dementia) and one in which chronic ischemic and infarction of smaller vessels results in clinical features attributable to damage to subcortical structures (subcortical dementia) [13]. Although helpful conceptually, these patterns are not always mutually exclusive, and it is not uncommon for patients to present with features of both types of dementias.

Cortical Dementia

Cortical dementia is caused by repeated infarcts (multi-infarct dementia) or single infarctions (strategic infarct dementia) of the large vessels supplying functionally important cortical brain regions. In VaD caused by multiple infarctions, the location, number, and volume of tissue damaged determines the pattern of cognitive and behavioral change [5]. Lesions involving the anterior, middle, or posterior cerebral arteries supplying large vascular territories can give rise to well-known dementia syndromes [14]. With injury to the left hemisphere, apahasias, apraxias, agnosias and elements of Gerstmann syndrome (agraphia, acalculia, left-right disorientation, finger agnosia) are often manifest while injury to the right hemisphere may result in neglect, confusion, aparaxias and constructional difficulties. Table 7.2 describes

Table 7.1 Subtypes of vascular dementia

Subtypes	Vessels involved	Common causes	Associated brain lesions
Strategic infarct dementia	Large and medium sized arteries and arterioles	Arterial occlusion due to thrombotic atherosclerosis or embolization	Single infarcts in functionally important areas: hippocampus, caudate, angular gyrus, thalamus
Multi-infarct dementia	Large and medium sized arterioles	Arterial occlusion due to thrombotic atherosclerosis or embolization	Multiple cortical or subcortical lesions (cortical, lacunar, microinfarcts)
Lacunar state (*etat lacunaire*)	Arterioles	Arteriolosclerosis, lipohyalinosis	Multiple lacunar infarcts in the basal ganglia and internal capsule
Subcortical leukoencephalopathy (Binswanger's disease)	Arterioles and small vessels	Arteriolosclerosis, lipohyalinosis, venous collagenosis	Lacunar infarcts in basal ganglia and frontal lobe white matter; diffuse white matter disease
Hypoperfusion dementia	Large arteries	Cardiac failure, carotid occlusion	Watershed infarcts, incomplete white matter infarcts, cortical laminar necrosis
Hemorrhagic dementia	Arteries, arterioles, veins	Arterial or venous rupture	Lobar or basal ganglia hemorrhage, subdural, subarachnoid, or intracerebral hemorrhage
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	Arterioles and small vessels	Notch 3 mutation	Lacunar infarcts in basal ganglia and frontal lobe white matter; diffuse white matter disease
Cerebral amyloid angiopathy	Arterioles and small vessels	Amyloid fragment deposition in arteries and arterioles	Lobar hemorrhage, microinfarcts, microhemorrhage, white matter lesions; typically spare basal ganglia

several of the well-known regional cognitive syndromes. The cognitive profile of post-stroke dementia is characterized by variable impairments across cognitive domains [15]. As a result, the term "patchy" is often applied to describe the cognitive pattern of severe deficits in certain domains and relative sparring of others. In cortical dementia, memory may be preserved, especially if the vascular supply to the medial temporal lobes is spared. Because the source of infarction is typically cardiac embolization or thrombotic atherosclerosis, symptom onset may be abrupt. If the primary motor cortex is spared, however, symptoms typically attributed to stroke may not be clearly noted. It is not uncommon for patients to stabilize or even improve after each stroke, resulting in a "stepwise" clinical course. With recurrent events, the vascular burden accrues and the dementia syndrome emerges.

Table 7.2 Cortical syndromes

Lateralization	Lesion	Possible symptoms
Left	Anterior cerebral	Akinetic mutism, disinhibition, abulia, apathy, executive dysfunction, callosal disconnection
	Middle cerebral	Aphasia, Gerstmann's syndrome (agraphia, acalculia, finger agnosia, right/left disorientation)
	Posterior cerebral	Alexia without agraphia, homonymous hemianopia
Right	Anterior cerebral	Apathy, abulia, executive dysfunction, behavior change, mania, callosal disconnection syndrome
	Middle cerebral	Hemineglect, anosognosia, constructional difficulty, confusion, agitation, visuospatial difficulty
	Posterior cerebral	Prosopagnosia, homonymous hemianopia

Subcortical Dementia

Subcortical dementia is caused by the cumulative effects of occlusive disease affecting the medium-sized arterioles and small vessels supplying the basal ganglia and subhemispheric white matter. Strongly associated with vascular risk factors, subcortical lesions are the most common lesions associated with VaD [9]. On MRI, small vessel disease is manifest as multiple lacunar infarcts (small noncortical infarcts measuring less than 1.5 cm) or areas of confluent white matter disease (also called leukoariaosis). Over time, the accumulated effect of these lesions is to disrupt subcortical and limbic circuits leading to a slowly progressive syndrome characterized cognitively by executive dysfunction, slowed mentation (bradyphrenia), and attentional deficits. Memory dysfunction is commonly manifest in subcortical dementia [16]. The pattern of memory loss is typically one of poor registration and inefficient retrieval rather than the "rapid forgetting" that is seen in AD. As a result, patients with subcortical VaD are more likely to benefit from hints or cues and perform better on recognition memory tasks [17]. Behavioral changes such as irritability, depression, and apathy are often among the most striking and earliest symptoms seen in subcortical dementia. The neurological examination of a patient with VaD due to subcortical injury is often described as "lower body parkinsonism" due to gait changes and falls. Patients often manifest with *marche a petit pas* ("gait with little steps"), a gait characterized by abnormally short, shuffled steps with upright stance and preserved arm swing. The face and upper extremities are typically less affected, however, careful examination of the upper extremities often reveals cogwheel rigidity or even spasticity. Another common feature of subcortical VaD is bladder dysfunction (frequency, urgency, and incontinence) not explained by urological disease. The triad of urinary incontinence, gait disturbance, and memory loss is more commonly produced by VaD than hydrocephalus [1].

Table 7.3 Neuropsychiatric symptoms associated with focal brain lesions

Symptom	Lesion
Apathy/abulia	Bilateral medial frontal
	Globus pallidus
	Medial thalamus
Disinhibition	Orbitofrontal
	Caudate
Depression	Left frontal
Anxiety	Left frontal
Obsessions and compulsions	Caudate
	Bilateral globus pallidus
Anosognosia	Right parietal
Mania	Right frontal

Neuropsychiatric Features

As in other dementia syndromes, neuropsychiatric symptoms are experienced almost universally in VaD [13] and represent a significant source of distress for both patients and their families. Apathy, depression, and abulia are considered hallmark neuropsychiatric features of subcortical VaD. Depression is frequently encountered after stroke with a cumulative incidence of 39–52% within 5 years of stroke [18]. Left frontal stroke is traditionally associated with an increased risk of post-stroke depression [19]. Other neuropsychiatric symptoms are experienced in VaD and may correlate to lesion location. Table 7.3 lists neuropsychiatric symptoms commonly associated with focal brain lesions. In comparison studies, patients with VaD experience more severe depression and apathy and are less likely to experience delusions or hallucinations than patients with AD [20].

Diagnostic Approach

Cognitive Screening

While cognitive deficits can be evaluated with questioning during the history, patients and family members often underestimate the severity of cognitive impairment and objective assessment of cognitive functioning is important. There are many bedside cognitive tests available to screen for dementia. The Mini-Mental Status Examination (MMSE) is the tool most commonly administered in the office setting. Designed to detect cognitive changes in AD, the MMSE lacks an assessment of executive function and is less sensitive to the early cognitive changes seen in VaD [21]. Other tests which more closely examine executive function, attention, and visuospatial function, such as the Montreal Cognitive Assessment (MoCA), are more likely to identify cognitive dysfunction in this population [22, 23]. The MoCA

includes a more detailed examination of memory (with sections on registration and both free and cued delayed recall) than the MMSE. The Vascular Dementia Assessment Scale (VADAS-cog) is another tool that has been used in clinical trials of patients with VaD and shows good sensitivity in patients even in patients with mild disease burden [24]. Deficits appreciated on screening tests can be further investigated with additional domain-specific tests and referral for neuropsychological evaluation.

Neuropsychiatric Assessment

Patients being evaluated for dementia should also be screened for neuropsychiatric symptoms as these symptoms often represent a significant source of distress for patients and families. Patterns of neuropsychiatric symptoms may also inform the differential diagnosis. The neuropsychiatric assessment can be supported by symptom rating scales, inventories and caregiver scales. Commonly used screening tools include the Neuropsychiatric Inventory Questionnaire (NPI-Q) [25], the Geriatric Depression Scale (GDS) [26], and the Behavioral Rating Scale for Dementia [27].

Functional Assessment

Assessment of activities of daily living is critical in a comprehensive evaluation of patients with dementia. Establishing a baseline is crucial in following the progression of disease and monitoring response to treatment. Accurate assessment of functional status will also direct both appropriate pharmacological and non-pharmacological interventions. Commonly used assessments include the Instrumental Activities of Daily Living Scale [28] and the Functional Activities Questionnaire [29].

Laboratory

There are no available blood or cerebral spinal fluid tests specific to the diagnosis of VaD. Laboratory testing can be used to rule out mimics (hypothyroidism, B12 deficiency), as well as to identify risk factors that may be contributing to cerebrovascular disease burden. Table 7.4 lists the laboratory tests that should be obtained in patients with suspected VaD. Homocysteine is particularly relevant in VaD due to its putative prothrombotic properties. Elevated homocysteine levels are associated with an increased risk of cerebrovascular disease and VaD [31, 32]. Vitamin supplementation with folate, B6, and B12 lowers homocysteine levels by about 20% [33] but has not been shown to prevent cognitive decline or improve cognition in VaD [34].

Table 7.4 Recommended laboratory screening in the initial workup of patients with VaD

Complete blood count
Comprehensive metabolic panel
Thyroid function panel
Homocysteine and methylmalonic acid
B1 (thiamine)
B9 (folic acid)
B12 (cobalamin)
Vitamin D
RPR/VDRL, HIV, hepatitis panel (if high level of suspicion)
Erythrocyte sedimentary rate
Inflammatory/autoimmune lab panel (if high level of suspicion)
Testosterone (in men with suggestive history) [30]

Neuroimaging

MRI and CT

Neuroimaging is essential for the diagnosis of VaD and required by most diagnostic schemes. All patients with clinical features suggestive of VaD—clinical stroke, focal neurological findings, abrupt symptom onset or stepwise disease course—should have neuroimaging. Although computed tomography (CT) scan may reveal large chronic infarcts or extensive white matter disease, magnetic resonance imaging (MRI) is the modality of choice as it provides better sensitivity in identifying smaller subcortical lesions not easily seen on CT. Unless there is increased suspicion of mass lesion or tumor, initial scans are usually obtained without contrast. The neuroimaging hallmarks of VaD include cortical infarcts, hemorrhage, lacunar infarcts, and white matter hyperintensities (also referred to as leukoaraiosis). Figure 7.1 shows several MRI findings commonly seen in VaD. Although there are no radiologic criteria for the diagnosis of VaD, the presence of dementia often correlates with overall vascular burden [10]. White matter hyperintensities seen on T2 or fluid attenuated inversion recovery (FLAIR) MRI sequences are commonly seen in both cognitively normal and demented populations and the interpretation of these lesions is not completely understood. Smooth periventricular rims and punctate lesions have less clinical significance than irregular confluent white matter hyperintensities, which, in elderly patients with vascular risk factors, are likely to represent a variety of vascular-mediated pathological processes (loss of myelin, microglial, and inflammatory changes) [35, 36]. White matter lesions have also been associated with demyelination, infection, neoplasms, and migraine, necessitating careful clinical correlation. In

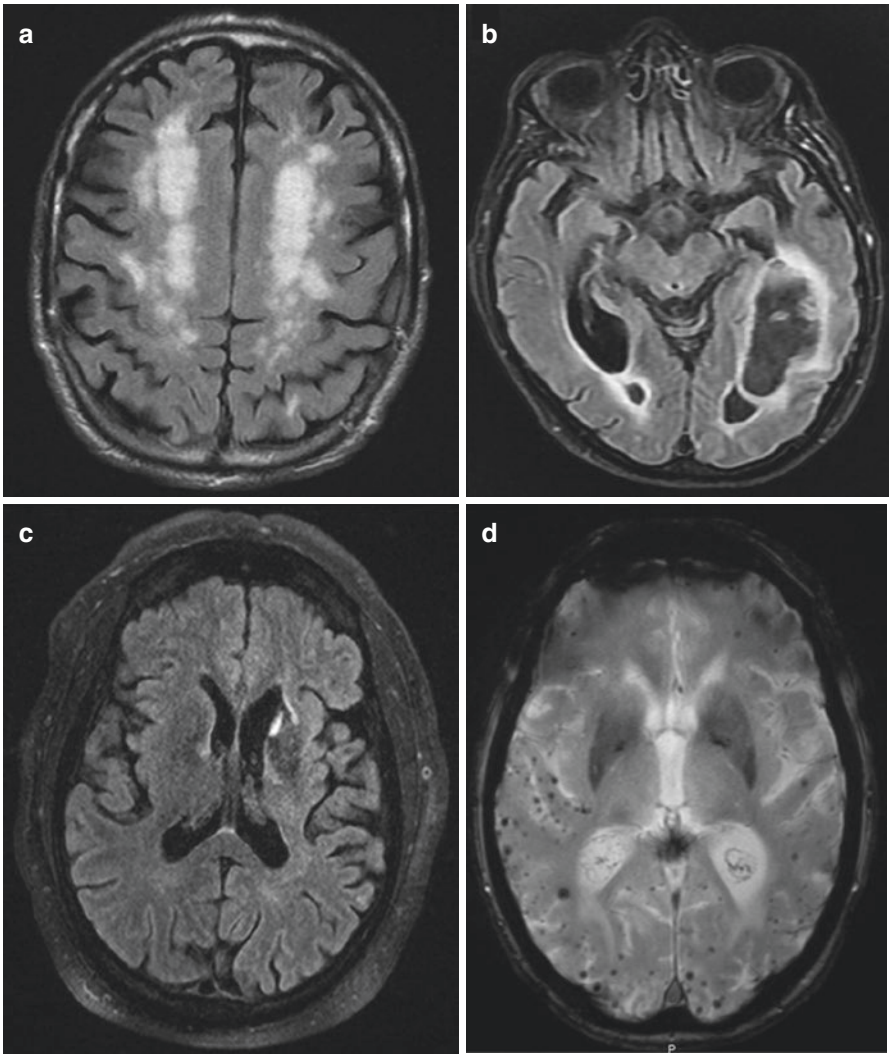

Fig. 7.1 MRI findings in VaD. (**a**) Confluent white matter changes related to small vessel disease on FLAIR imaging sequence in a patient with Binswanger's disease. (**b**) Left temporal-parietal lobar hemorrhage with subsequent alexia as a striking cognitive deficit on FLAIR imaging sequence. (**c**) Left caudate infarct in a patient with strategic infarct dementia resulting in executive dysfunction following disruption of frontal subcortical circuits on FLAIR imaging sequence. (**d**) Multiple cortical microhemorrhages in a patient with cerebral amyloid angiopathy on a T2* sequence

clinical trials and research studies, radiologic evidence of 25% involvement of cerebral white matter is often used as a threshold to identify VaD [2].

Microinfarcts are increasingly recognized as significant contributors to cognitive dysfunction in dementia populations. In the Religious Orders Study, the presence of microinfarcts was associated with increased risk of dementia and reduced speed and poorer memory performance on cognitive testing. This is of particular relevance because microinfarcts fall below the resolution of currently used 1.5 and 3 T MRI and approximately 50% of people with microinfarcts do not have macroinfarcts [37]. Improving the diagnostic sensitivity of VaD remains a major goal in the field [36].

FDG-PET and Amyloid Imaging

Fluorodeoxyglucose positron emission tomography (FDG-PET) is not routinely obtained in the evaluation of VaD as structural imaging is usually adequate for diagnosis. FDG-PET may be useful in confirming the presence of concurrent neurodegenerative pathologies. Certain patterns of hypometabolism: parietal and posterior cingulate in AD; frontotemporal in FTD; and mesial occipital cortex in DLB, should alert the clinician to the likely presence of a mixed syndrome.

Amyloid PET is available as a means of excluding AD as a contributing factor in a patient with suspect VaD (Fig. 7.2) or as means of supporting the presence of AD in a patient with mixed dementia.

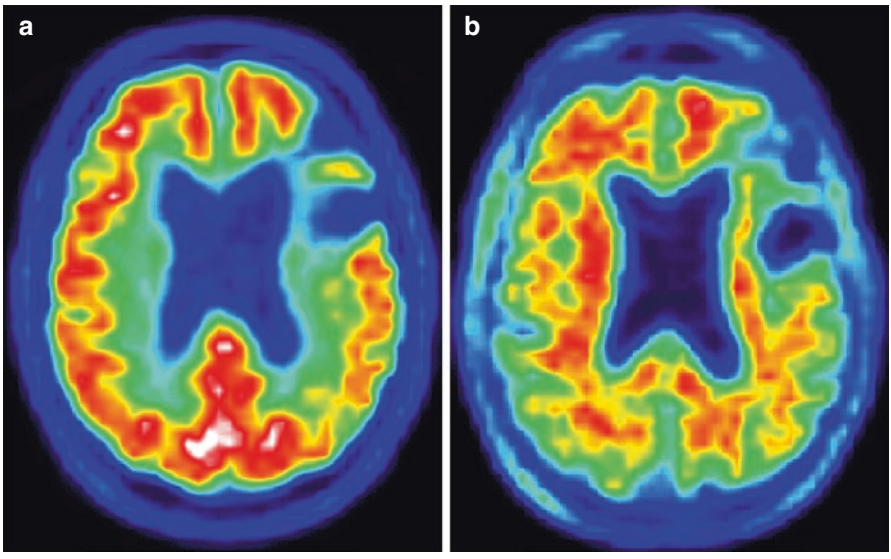

Fig. 7.2 FDG PET (**a**) (*left*) in a patient with VaD and no AD as shown by negative amyloid imaging (**b**) (*right*)

Electrophysiology

Electrophysiology is neither sensitive nor specific in the diagnosis of VaD. Stroke, however, is the most common antecedent factor for the development of epilepsy in adults [38]. "Red flag symptoms" suggestive of seizure disorder overlap considerably with the symptoms of VaD and include abrupt and stereotyped changes in behavior, repeated episodes of incontinence, and fluctuating cognition. A low threshold of clinical suspicion should lead to obtaining an electroencephalogram (EEG).

Genetic Testing

Genetic testing is of limited value in older patients (>65 years of age) with VaD. In younger patients presenting with VaD, a rare but important cause is cerebral autosomal dominant arteriopathy (CADASIL). This disorder is caused a mutation in the NOTCH/3 gene on chromosome 19. Patients with CADASIL develop extensive lacunar infarctions and white matter disease before the age of 60 (Fig. 7.3). Inheritance is autosomal dominant. Common features associated with CADASIL include migraine with aura, repeated TIAs, and seizures. White matter lesions involving the anterior pole of the temporal lobe are distinct features of CADASIL and rarely seen in patients with ischemic disease [39]. A commercially available test is available to test for the NOTCH/3 mutation and should be considered for appropriate patients.

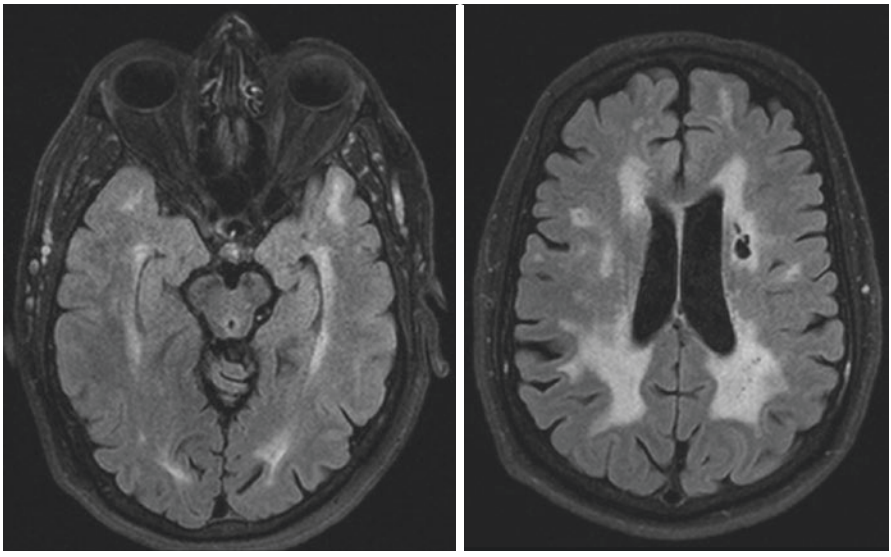

Fig. 7.3 MRI of 57 year old male with CADASIL

Table 7.5 Characteristic patterns of cognitive impairment in dementing disorders

Syndrome	Cognitive deficits
Alzheimer's disease	Memory (encoding, retrieval, recognition)
	Executive function
	Visuospatial deficits
Frontotemporal dementia	Executive function
	Variable language impairment
Dementia with Lewy bodies	Attention and concentration
	Visuoperceptional deficits
	Visuoconstructional deficits
Vascular dementia	Attention and concentration
	Memory (retrieval)
	Executive function

Neuropsychological Testing

Formal neuropsychological testing provides reliable information on a patient's cognitive functioning. This can be valuable in the care of VaD as it can be used to track the evolution of cognitive deficits over time and to monitor response to treatment. Testing can also be used to aide in the differential diagnosis given the different patterns of cognitive deficits seen in other dementing disorders. Table 7.5 summarizes the different patterns of neurocognitive performance among the various dementia syndromes. The neuropsychological pattern of AD overlaps considerably with VaD, however, differences in memory impairment—in AD memory deficits are seen in encoding and retrieval while in VaD deficits are primarily seen in retrieval—and executive function (greater impairment in VaD than AD) may be helpful in distinguishing the two [40].

Not all patients should be referred for formal neuropsychological testing. Neuropsychological testing is most helpful early in the course of illness when it is often difficult to distinguish from normal aging or when bedside screening tests fail to demonstrate the presence of deficits. The utility of neuropsychological testing in patients with moderate to advanced dementia is limited as performance on cognitive deficits is at "floor" levels.

Diagnostic Criteria

Several different clinical criteria for VaD have been proposed. A significant barrier in validating these criteria is the lack of standardized pathological criteria for VaD and the high co-occurrence of other pathologies in those with cerebrovascular disease. Earlier iterations of the diagnostic criteria for VaD required the presence of

Table 7.6 American Heart Association/American Stroke Association statement on vascular contributions to cognitive impairment and dementia clinical criteria for diagnosis of vascular dementia [4]

A diagnosis of probable vascular dementia requires either:
1. A clear temporal relationship between a vascular event and onset of cognitive deficits
or
2. A clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular pathology
and
3. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder
A diagnosis of possible vascular dementia requires imaging evidence of cerebrovascular disease but:
1. There is no clear relationship between the vascular disease and cognitive impairment **or**
2. There is insufficient information for the diagnosis of VaD **or**
3. Severity of aphasia precludes proper cognitive assessment **or**
4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition

memory impairment for the diagnosis of dementia, a cognitive feature that is not always present in patients with VaD. In an attempt to recognize the broad contributions of vascular lesions on cognitive function from all causes (multi-infarct, subcortical, hemorrhagic), the more inclusive term of vascular cognitive impairment (VCI) has been introduced [4]. VCI captures the entire spectrum of cognitive impairment from mild impairment to dementia. The criteria also recognize the contribution of cerebrovascular disease to mixed dementia syndromes. For dementia due to VCI, at least two cognitive domains must be impaired and patient must meet functional impairment criteria for dementia (Table 7.6).

Differential Diagnosis

Clinically, the differential diagnosis of VaD includes other causes of cognitive impairment in the elderly including AD, Parkinson's disease, normal pressure hydrocephalus (NPH), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), human immunodeficiency virus (HIV) dementia, cerebral amyloid angiopathy (CAA), and Creutzfeldt-Jakob disease (CJD). These conditions can often be reliably excluded by correlating findings from the clinical examination to vascular lesions on neuroimaging. Figure 7.4 provides an approach to differential diagnosis. The Hachinski Ischemic Score (HIS) was initially established to distinguish multi-infarct dementia from AD and has historically been used to distinguish multi-infarct dementia from other dementia syndromes (Table 7.7). In a large meta-analysis including only studies with pathological

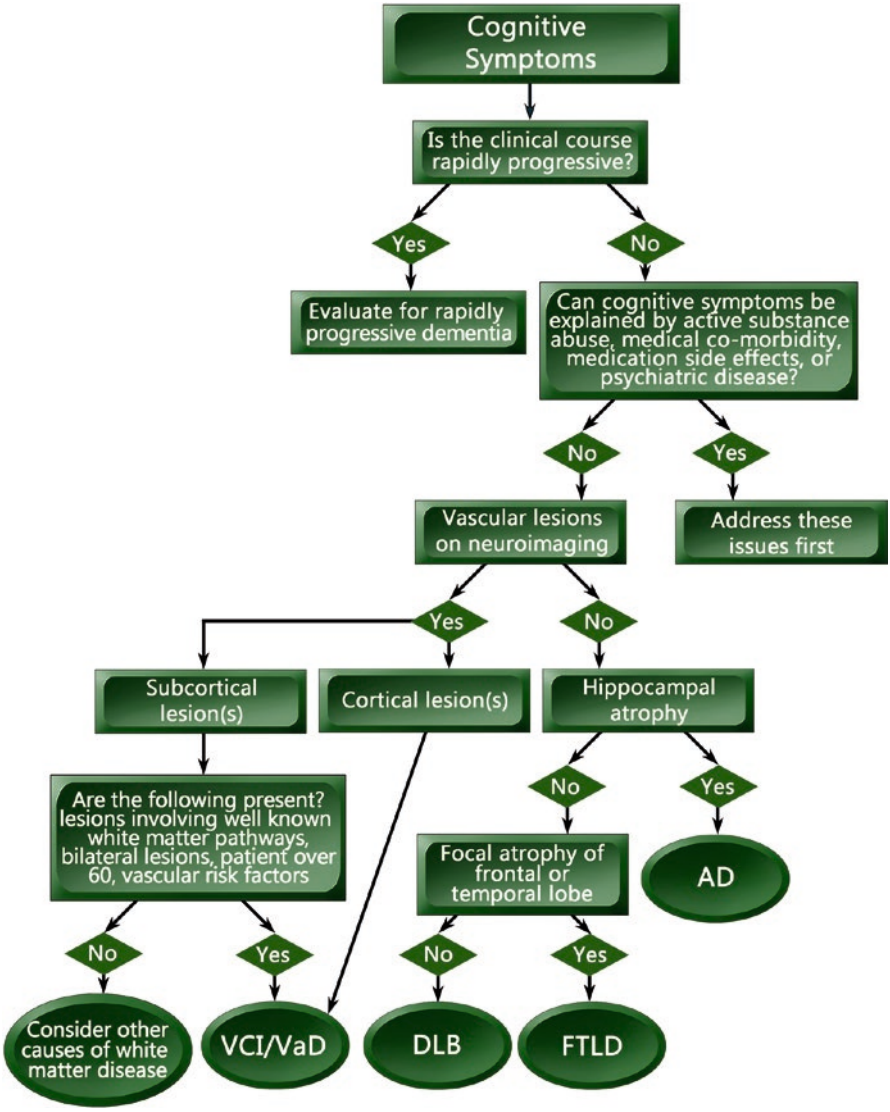

Fig. 7.4 Approach to dementia differential diagnosis

verification, a score of 7 or greater on the HIS had a sensitivity and specificity of 90% for VaD [41]. The HIS does not reliably distinguish pure VaD from mixed syndromes.

Table 7.7 Hachinski Ischemic Score

Symptom	
Abrupt onset	+2
Fluctuating course	+2
History of stroke	+2
Focal neurological symptoms	+2
Focal neurological signs	+2
Stepwise deterioration	+1
Nocturnal confusion	+1
Preservation of personality	+1
Depression	+1
Somatic complaints	+1
Emotional incontinence	+1
Hypertension	+1
Associated atherosclerosis	+1
Scores of 4 or lower suggest AD	
Scores of 7 or higher suggest VaD	

Table 7.8 Other causes of extensive white matter disease

Leukodystrophies	Metachromatic leukodystrophy, adrenoleukodystrophy, globoid cell leukodystrophy, cerebrotendinous xanthomatosis
Inflammatory disorders	Multiple sclerosis, systemic lupus erythematous, sarcoidosis
Toxic or metabolic disorders	Cranial irradiation, solvent exposure, carbon monoxide poisoning, B12 deficiency, Marchiafava-Bignami disease
Neoplasms	Gliomatosis cerebri, primary cerebral lymphoma

The widespread white matter changes associated with subcortical VaD must be distinguished from non-ischemic causes of white matter hyperintensities on MRI. Some disorders causing non-ischemic white matter disease may also present with a progressive cognitive and behavioral impairment. The differential diagnosis for extensive subcortical white matter disease is large and includes the adult-onset leukodystrophies, infectious disorders, multiple sclerosis, inflammatory diseases, toxic or metabolic disorders, hydrocephalus, and neoplasms (Table 7.8). The characteristic appearance of white matter hyperintensities due to ischemic causes include confluent areas that are often bilateral and symmetrically located in the hemispheric white matter [42]. They are most commonly symmetrical, supratentorial, and periventricular [43]. Figure 7.5 provides an approach to assessing VCI.

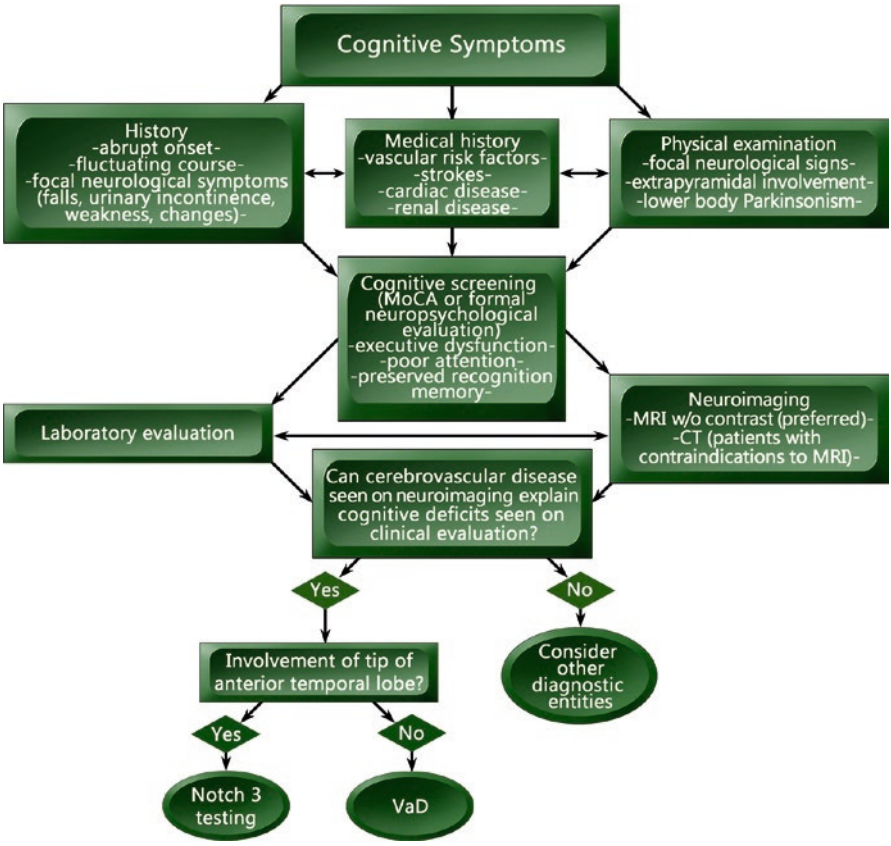

Fig. 7.5 Assessment of VCI

Management

Currently there are no therapies that can reverse the cerebrovascular damage that causes VaD. The primary objective of pharmacologic management of VaD is thus directed at preserving cognitive stability. The two dimensions of VaD pharmacology include [3] prevention of recurrent vascular disease through management of risk factors for cerebrovascular disease and [4] symptomatic treatment of the cognitive and neuropsychiatric symptoms that arise during the course of disease. Figure 7.6 provides a guide to treatment of VCI/VaD.

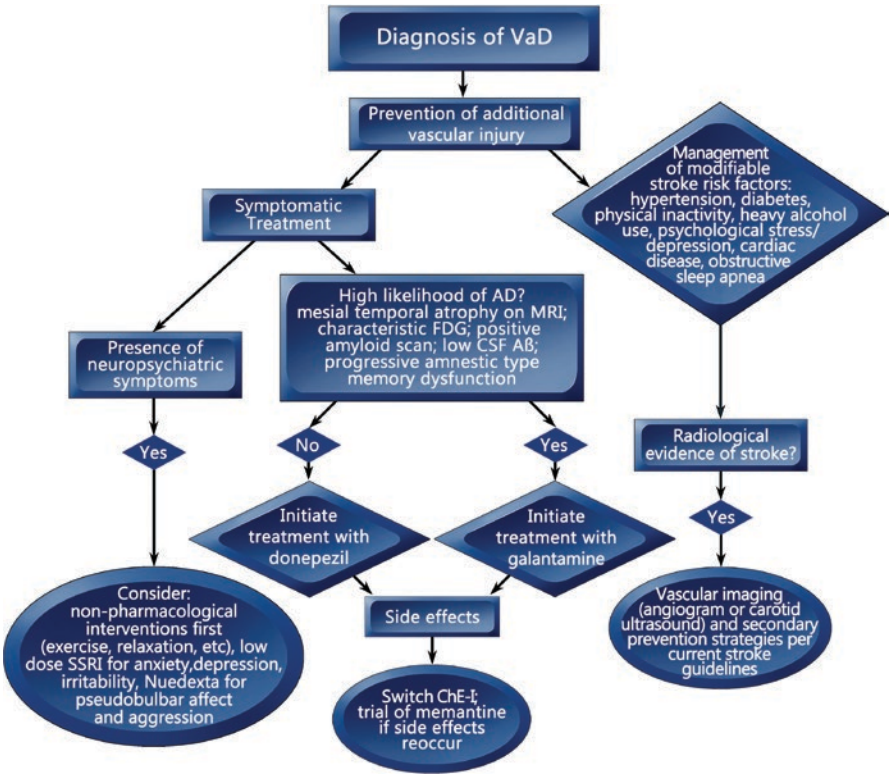

Fig. 7.6 Approach to treatment of VCI/VaD

Risk Factor Management

Because slowing or preventing additional vascular injury is critical to disease course and prognosis in VaD, addressing modifiable risk factors for cerebrovascular disease is the most efficient management strategy for VaD. Patients with VaD should be carefully screened for hypertension, impaired fasting glucose, heavy alcohol or drug use, atrial fibrillation, hyperlipidemia, kidney disease, and obstructive sleep apnea. Table 7.9 lists the modifiable risk factors associated with cerebrovascular disease [44]. Treatment of risk factors should take a measured approach in the elderly as optimal blood pressure and cholesterol targets have not been established in those over 80 years of age. Careful management of blood pressure and glucose

Table 7.9 Modifiable risk factors for stroke [44]

Hypertension
Current smoking
Obesity
Diet
Physical inactivity
Diabetes
Heavy alcohol use
Psychological stress
Depression
Cardiac disease

levels is crucially important, as hypoglycemia and hypotension have been associated with dementia [45] [46]. Although risk factor modification has not been shown to overcome cognitive impairment in VaD, prevention strategies are important for reducing the risk of recurrent stroke [47]. Secondary prevention strategies (platelet anti-aggregants, anti-coagulants, etc) should be recommended as indicated by stroke specific guidelines [47]. Platelet anti-aggregants and antithrombotics are associated with a higher risk of bleeding in patients with cerebral amyloid angiopathy and should be avoided unless there is a compelling indication [48]. There have been few studies of lifestyle changes (healthy diets, smoking cessation, cognitive engagement, and regular exercise) and medical interventions (blood pressure and lipid control) in subjects with established VaD, however, emerging evidence suggests that these strategies may be promising strategies for preventing cognitive decline, especially when initiated in midlife [49]. Healthybrains.org provides guidance for brain healthy lifestyle choices.

Vascular Studies

When cerebral infarction occurs or is identified on neuroimaging, evaluation to define specific subtypes and etiology should be initiated following current guidelines. Evaluation of carotid vessels with ultrasound or vascular imaging should be pursued when vascular lesions are noted in characteristic regions. Cardiac imaging and prolonged heart monitoring should be pursued in patients with multiple infarcts suggestive of a cardioembolic etiology.

Sleep Studies

The effects of obstructive sleep apnea (OSA) on cognitive dysfunction are increasingly recognized [50]. Recently, associations between lower oxygen saturations on polysomnography and microhemorrhages have been reported [51]. Obstructive

sleep apnea is a known risk factor for stroke and death from all causes [52]. All patients being evaluated for VaD should be screened for symptoms suggestive of sleep apnea including snoring, daytime sleepiness, morning headaches, mood changes, witnessed apneas by bed partner, and nocturia. A low threshold of clinical suspicion should prompt further evaluation by a sleep specialist.

Driving Assessment

In light of early deficits in attention, executive, and/or processing speed, a driving history should be obtained from all patients being evaluated for VaD. A history of recent violations or accidents, family members' reports of feeling unsafe, or reckless behavior should be referred for further evaluation. Physical exam or cognitive assessment of significant visuospatial or executive dysfunction should also prompt referral. The American Academy of Neurology has published practice parameters for the evaluation and management of driving risk in dementia [53].

Symptomatic Treatment

Alzheimer's Disease Agents

In clinical studies, cholinesterase inhibitors (ChE-Is) have demonstrated small but significant benefits on cognition in VaD [2]. Because benefits have not been noted in global functioning or activities of daily living they have not been granted regulatory approval for use in VaD. Although many experts argue that the cognitive benefits of these agents seen in clinical trials is likely due to the presence of concurrent AD pathology in VaD cohorts, there is experimental and pathological evidence of cholinergic dysfunction in VaD independent of AD pathology [54]. There is also evidence that ChE-Is improve cerebral blood flow [55], providing an additional rationale for using these agents in VaD. Current guidelines suggests that patients with "pure" VaD may benefit from a trial of donepezil while patients with "mixed" VaD/AD may benefit from a trial of galantamine [4]. Rivastigmine and memantine have also demonstrated benefits on cognition in VaD in smaller, less well-constructed trials. Further study is required to establish whether these agents are beneficial in VaD. Table 7.10 summarizes the current symptomatic therapies for VaD.

Table 7.10 Therapies to improve cognition in VaD

Name	Metabolism	Starting dose (mg)	Therapeutic dose (mg)	Population studied	Benefit seen
Donepezil	Hepatic	5–10	5–10	"pure" VaD	Cognition
Galantamine	Hepatic	8	16–24	"mixed" VaD	Cognition

Psychotropic Agents

Despite a high prevalence of neuropsychiatric symptoms, there is little evidence to guide treatment of these symptoms in VaD populations. Clinical experience and the disability associated with these symptoms suggest that neuropsychiatric symptoms in VaD can be managed using the same cautious approach used in AD (see Chap. 23).

ICD-10 Codes

Vascular dementia without behavioral disturbance F01.50.
Vascular dementia with behavioral disturbance F01.51.

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