

Vascular Dementia

Vascular Dementia. An investigation into a “new” disease.

As medical students, we all encounter unique patients and new challenges each day. Some you may have a good idea of what is going on and others make you scramble for a book! All of these challenges are exciting. Recently I had a patient with symptoms I had never seen before. Cognitive deficits, memory loss and a pathology filled head CT. I was intrigued. What could this be? Quickly some degree of a differential sparked in my head. After an investigation, a diagnosis, and treatment, the patient was discharged. I learned about a devastating disease and how it can affect not only one life, but many. This disease is Vascular Dementia.

What is Vascular Dementia?

Vascular Dementia (VaD) is an etiologic category that includes clinical forms of dementia caused by ischemic or hemorrhagic cerebrovascular disease (CVD) or by ischemic-hypoxic brain lesions of cardiovascular origin. (1)

Quick Background

In 1894, Otto Binswanger and Alois Alzheimer separated VaD from dementia paralytica (neurosyphilis), a common cause of dementia at that time, and identified at least four different clinicopathologic forms of VaD. (1) More recently, in 1974, Hachinski coined the phrase multiinfarct dementia. In 1985, Loeb used the broader term vascular dementia. Currently, with the introduction of new-generation CT and MRI of the brain, details, such as the role of ischemic-hypoxic white matter lesions in the pathogenesis of VaD, can be distinguished. (1)

How does the Pathophysiology of VaD work?

Five subtypes of VaD have been described. They include (1) multiinfarct dementia, (2) vascular dementia due to a strategic single infarct, (3) vascular dementia due to lacunar lesions, (4) vascular dementia due to hemorrhagic lesions, and (5) Binswanger disease.

Vascular dementia can be further classified as cortical, subcortical, and mixed dementia (combination of AD and vascular dementia). (2)

Vascular disease produces either focal or diffuse effects on the brain. Focal CVD occurs secondary to thrombotic or embolic vascular occlusions. Hypertension is the major cause of diffuse disease, and, in many patients, both focal and diffuse disease is observed together. (2) In addition, depending on the location of the infarct, different brain circuits may be interrupted. For a more detailed look at the location and result of brain circuitry lesions, see **Appendix-1**.

The elderly are most susceptible to ischemic lesions of small vessels. This may result in lacunar, cortical microinfarcts (granular atrophy), and Binswanger disease. (1) Small-vessel disease can also result in arterial wall changes, expansion of the Virchow-Robin spaces, and perivascular parenchymal rarefaction and gliosis. (2) Ageing

produces tortuosity and elongation of these arterioles. While narrowing of the lumen can be produced by senile arteriolosclerosis, diabetes, and hypertension. These morphologic changes result in the loss of the normal autoregulation of cerebral blood flow and thus, hypoperfusion of gray matter and white matter. (1)

Lacunar disease is due to small-vessel occlusions, and typically produces small cavitory lesions within the brain parenchyma. Binswanger disease (BD) (otherwise known as subcortical leukoencephalopathy) is due to diffuse white-matter disease. In Binswanger disease, vascular changes observed are fibrohyalinosis of small arteries and fibrinoid necrosis of the larger vessels inside the brain. (2)

How Common is VaD ?

Together AD and VaD are the most common causes of senile dementia. (1) Individually, VaD is the second most common cause of dementia in the United States, behind Alzheimer Dementia (AD). (1,2) It has been estimated that, prevalence rates of VaD double every 5.3 years compared with every 4.5 years for AD. (1)

VaD is reportedly more common in men in contrast to AD, which is more often in women. Also, VaD has a peculiar geographic (racial) variation, being more prevalent in Asian populations than in white populations. This is most likely a result of the preponderance of small vessel disease in Oriental races. (1) In addition, the prevalence rate of dementia is 9 times higher in patients who have had a stroke than in controls. (2)

Poststroke dementia is the most common form of VaD. It has been reported that in the United States alone, approximately 125,000 new cases of VaD after ischemic stroke occur every year (approximately one third of the estimated 360,000 incident cases of AD). (1,3)

What are the Risk factors for vascular dementia?

Pohjasvaara and colleagues confirmed that the most important risk factors for poststroke VaD are older age, lower educational level, recurrent stroke, and left hemisphere stroke (associated with a fivefold increase), as well as the presence of dysphagia, gait limitations, and urinary impairment. (4) Moreover, the presence of hypoxic and ischemic complications of acute stroke, such as seizures, cardiac arrhythmias, or aspiration pneumonia, is strong and independent risk factors for development of poststroke dementia. (1) In addition, stroke volumes consisting of larger than 50–100 ml of tissue destruction has been linked to VaD development. (1) Although a cause of stroke, high intakes of total, saturated, and trans fat and cholesterol have not been associated with increased risk of dementia or its subtypes. (1)

How do patients with Vascular Dementia present?

Clinical forms of vascular dementia.

Cognitive impairment, acutely or subacutely, after an acute neurological event with a stepwise progression is a typical history suggestive of vascular dementia. However, this typical history usually is observed in multiinfarct dementia and may not be seen with lacunar infarcts. Also patients with VaD may present with severe depression, psychotic symptoms, predominantly the delusional type, have been described. Lateralizing signs may also be present in VaD. These include hemiparesis, bradykinesia, hyperreflexia, extensor plantar reflexes, ataxia, pseudobulbar palsy, and gait and swallowing difficulties. (2)

Differential Diagnosis

Table-1 lists the major diseases in the Differential Diagnosis (DD) of VaD and their accompanying signs and symptoms.

Table-1. Major causes of Dementia and their associated clinical presentation

Disease	Clinical Signs and Symptoms
VaD	Patchy cognitive impairment, often with focal neurological signs and symptoms. Onset may be abrupt, with a stepwise decline
AD	Early language, short-term memory, and visuospatial deficits, Usually, no motor findings are present until the middle or late stages of the disease
Parkinson dementia	Cognitive slowing with extrapyramidal signs – cog-wheel rigidity, bradykinesia, tremor, and gait disturbances. Usually, dementia is seen in later stages of the disease.
Dementia due to head trauma	Memory impairment and other cognitive deficits associated with a history of head trauma. Not progressive unless the person has a history of repeated head trauma (eg, dementia pugilistica)
HIV dementia	Cognitive changes with neurological signs and a positive HIV test
Pick disease	Memory problems, personality changes, and deterioration of social skills, 5 th or 6 th decade of life. Frontal-release signs such as snout and grasp reflex may also be present.
Huntington’s disease	Autosomal dominant. Onset of cognitive changes as early as the third decade, with physical signs of choreoathetosis
Creutzfeldt-Jakob disease	Onset is between the fourth and sixth decades and is associated with myoclonus, seizures, and ataxia. A rapid progression is typical.
Lewy body dementia	Recurrent visual hallucinations, fluctuating cognitive impairment, and parkinsonism features.
Pseudodementia	Cognitive and mood symptoms secondary to depression, poor memory function, acute onset, patients answer “I don’t know” often without thinking, also termed dementia of depression

Subacute (subcortical) vascular dementia

The temporal profile of presentation of these forms of VaD is typically subacute, with a chronic course marked by fluctuations and progressive worsening. The main forms of subacute subcortical VaD are leukoencephalopathy (CADASIL), lacunar state (*état lacunaire*), and Binswanger disease. (1)

One of the most important recent developments in the field of VaD has been the clinical and genetic description of *Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy*, also known as CADASIL. CADASIL is an autosomal dominant disorder of cerebral small vessels mapped to chromosome 19q12. Clinical manifestations include transient ischemic attacks and strokes (80%), cognitive deficits and VaD (50%), migraine with focal deficits (40%), mood disorders (30%), and epilepsy (10%). (1)

Other specific types of VaD include, Lacunar state and Binswanger type dementia. (1) Their clinical manifestations are similar, and are discussed jointly. A lacunar state and BD produce 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, and difficulties with set

shifting. Mood and behavioral changes are observed early and, in some patients, may be the presenting feature. (2)

How is a diagnosis of VaD confirmed?

Distinguishing VaD from AD

When VaD is clinically suspected there are a series of tests that can be administered to confirm or rule out the disease. These tests include cognitive screening exams, neuropsychological testing, lab and imaging studies. The most commonly used cognitive screening exam is the Folstein Mini-Mental State Examination (See **Appendix-2**). This test should be considered for the detection of dementia in individuals with suspected cognitive impairment. (5) The results of the test are variable, but in general, VaD presents with patchy defects, while in AD, the deficits will be global. Clock drawing may also be useful as an adjuvant test for VaD evaluation. Patients with VaD will often have significant difficulties illustrating a clock and proper time. In addition, multiple more specific diagnostic criteria can be used to diagnose vascular dementia, including the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria (**Table- 2**), and the *International Classification of Diseases, Tenth Edition (ICD-10)* criteria. (2)

TABLE 2 -- DSM-IV Diagnostic Criteria for Vascular Dementia
A. The development of multiple cognitive deficits manifested by both
1. memory impairment (impaired ability to learn new information or to recall previously learned information)
2. one (or more) of the following cognitive disturbances:
a. aphasia
b. apraxia
c. agnosia
d. disturbance in executive functioning
B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning
C. Focal neurological signs and symptoms
D. The deficits do not occur exclusively during the course of a delirium

Adapted from Goetz: Textbook of Clinical Neurology, 2nd ed.,2003 Elsevier Chapter 22, p. 422. *OR (Love BB, Biller J. Chapter 22: Neurovascular System. In: Goetz CG, Pappert EJ eds. Textbook of Clinical Neurology. Philadelphia: Saunders, 2003:395-424.)

Neuropsychological Testing can also be used to characterize dementia. Patients with VaD have patchy neuropsychological deficits. With vascular dementia, patients have better free recall and fewer recall intrusions compared to patients with AD. Apathy seen early in the disease is more suggestive of VaD because it usually is seen in the later stages of AD. Patients with vascular dementia have poor verbal fluency and more perseverative behavior when compared to patients with AD. They may even have other signs of executive dysfunction such as cognitive slowing, difficulty in shifting sets, and

problems with abstraction. (3) Likewise a meta-analysis, found the following features more often in VaD than in AD: stepwise deterioration, fluctuating course, history of hypertension, history of stroke, and focal neurologic symptoms. (6)

During the workup of dementia laboratory testing should be performed. This is done to rule out other causes of dementia. These tests should include CBC count, erythrocyte sedimentation rate, glucose level, renal and liver function tests, serological tests for syphilis, vitamin B-12 and red blood cell folate levels, and thyroid function tests. If suspected, serological testing for HIV, lupus anticoagulant, antiphospholipid antibody, and antinuclear antibody may be performed. (2)

Imaging

Neuroimaging studies include CT and MRI brain scans (**Figure-1**).

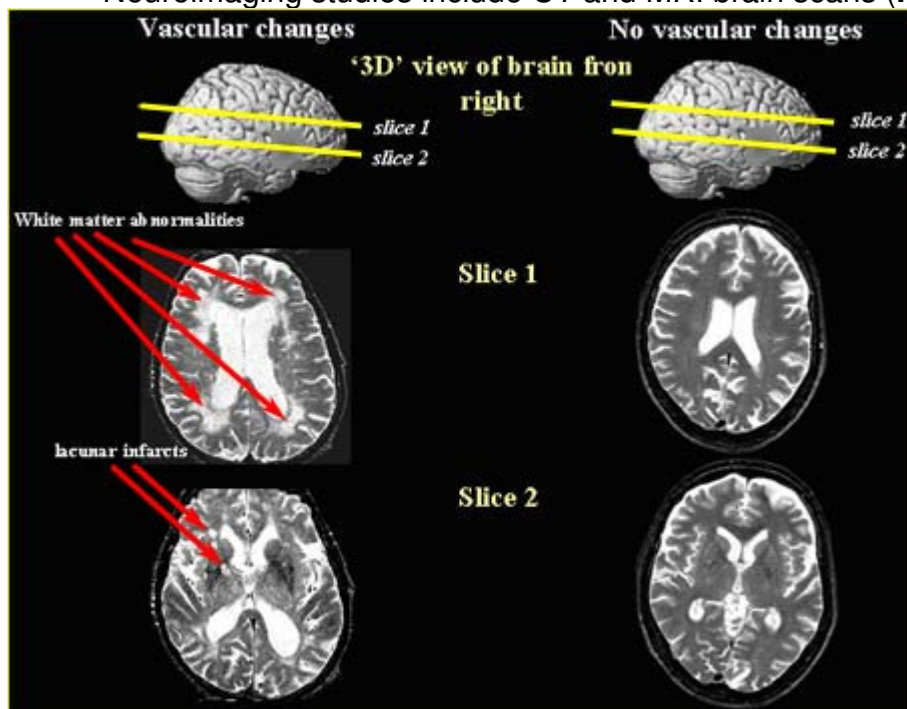


Figure 1. MRI from patients with (left) and without (right) abnormalities of the type seen in VaD. Images on the bottom are single MRI 'slices' through the brain. The top images are three dimensional views of the brain, with the yellow lines denoting the location of the slices below. Picture adapted from http://memory.ucsf.edu/Education/education_vad.html.

By definition, absence of vascular lesions on brain imaging excludes VaD. (1) Findings on CT scan or MRI that are suggestive of VaD are bilateral multiple infarcts located in the dominant hemisphere and limbic structures, multiple lacunar strokes, or periventricular white-matter lesions extending into the deep white matter. Mungas et al 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. (7) Another study comparing serial MRI images of VaD, AD, and Lewy body dementia found that the rate of atrophy was increased in all three dementia groups compared with control subjects. However no significant differences were seen between the groups. (8) PET (positron emission tomography) imaging has also been used to differentiate VaD from AD. (2)

Once identified, how is VaD treated?

Because the cause of VaD is a consequence of CVD, treatment of VaD has focused on controlling the risk factors for CVD development. (2, 9,10) Similarly, there are currently no FDA-approved treatments specifically for VaD. (9) Therefore, management and modification of lifestyle factors are crucial, including the elimination of cigarette smoking, weight reduction, nutritional education, and treatment of hypercholesterolemia and hypertriglyceridemia. (9,10)

The mainstay of VaD treatment is the prevention of new strokes. This includes using antiplatelet drugs and controlling major vascular risk factors. Antiplatelet agents are often prescribed to help prevent recurrent stroke. For example, Aspirin has been found to slow the progression of vascular dementia. (2) Additional antiplatelets include Ticlopidine (Ticlid) which is used in patients who cannot tolerate aspirin therapy or in whom aspirin therapy fails, and Clopidogrel bisulfate (Plavix). (2)

Other drugs used in the treatment of VaD include Neuroprotective drugs such as nimodipine and propentoxifylline, Memantine, and Cholinesterase inhibitors. (1,2) Nimodipine (Nimotop) has demonstrated moderate efficacy in tests of attention and psychomotor performance in the subcortical (small vessel) form of VaD. This agent has an effect on autoregulation of cerebral blood flow and blocks L-type calcium receptors, providing some degree of neuroprotection. (1) *Pentoxifylline (Trental)* is a xanthine derivative with hemorheologic properties (1). Hemorheologic drugs improve the flow properties of the blood by lowering the viscosity, improving the erythrocyte flexibility, inhibiting platelet aggregation and thrombus formation, and suppressing leukocyte adhesion (2). However, most studies using Pentoxifylline are small and need further characterization (1, 2).

Memantine is a potent noncompetitive antagonist of the N-methyl-D-aspartate receptor with nootropic (cognition improving) properties. Memantine has been shown to be well tolerated and useful in severe dementia and has very few side-effects. (11) Also, there is evidence of improvement in cognition in patients treated with memantine, especially in those with more advanced disease. (11)

There has been encouraging results obtained with the use of cholinergic agents in the treatment of VaD. (1,12) Cholinergic drugs are believed to be effective in VaD because in many cases these patients have cholinergic deficits related to ischemic involvement of basal forebrain neurons such as the nucleus basalis of Meynert. (1) Of the available cholinergic agents approved for the treatment of AD, donepezil hydrochloride (Aricept), rivastigmine tartrate (Exelon), and galantamine hydrobromide (Reminyl) have been used in patients with VaD. (1) More recently, the potential use of cholinesterase inhibitors and memantine in VaD has been promising. (12)

Supplementary drugs include atypical antipsychotic drugs. For example, risperidone and olanzapine, have been useful in the treatment of agitation and disruptive behaviors. For some patients with depression and anxiety, the use of antidepressants, such as the selective serotonin reuptake inhibitors citalopram or sertraline, may be required. (1,2)

What is the Follow up and Outcome of patients with VaD?

Regular follow-up every 4-6 months is recommended to assess the patient's general condition and cognitive and noncognitive symptoms. Frequent visits may be needed for patients with behavioral problems and patients who are on specific therapies

such as neuroprotective agents. Treatment of risk factors such as hypertension, hypercholesterolemia, and diabetes require special attention. (2)

It has been estimated that vascular dementia shortens life expectancy by approximately 50% in men, in persons with lower education, and in persons who perform worse in neuropsychological testing. Frequently arising ethical issues and dilemmas in the care of individuals with vascular dementia include: dementia and driving consent for treatment and care and Issues of end-of-life care, including artificial nutrition and hydration. (2)

The Med Students Pocket Summary:

- VaD is defined as the loss of cognitive function resulting from ischemic, ischemic-hypoxic, or hemorrhagic brain lesions as a result of CVD and cardiovascular pathologic changes.
- VaD is the second most common cause of dementia in the elderly after AD.
- VaD may be caused by multiple strokes or by a single strategic stroke, such as a lacune.
- Diagnosis requires (1) cognitive loss (often predominantly subcortical), (2) vascular brain lesions demonstrated by imaging, and (3) exclusion of other causes of dementia, such as AD.
- VaD is excluded by brain imaging showing no evidence of vascular lesions.
- Consider AD, Parkinson’s, Head Trauma, HIV, Pick’s, Huntingtons, Lewy body, and Pseudodementia in the DD for VaD.
- Treatment of VaD includes the prevention of strokes and the control of CVD risk factors- Aspirin 325 mg PO qd or Ticlid 250 mg PO bid
- Anticholinergic medications may be used for VaD
- Atypical antipsychotic agents and antidepressants (eg, selective serotonin reuptake inhibitors) may be required in some patients

Quick overview of Diagnostic Work-up for Dementia
History
Patient and corroborating historian
Emphasis: Past history of vascular events, hypertension, head trauma, medications, substance abuse, sexual history, family history of dementia
Physical examination
Emphasis: Comorbid conditions; vascular, neurologic, cognitive function (MMSE, clock drawing, ADAS-Cog); physical/functional status (Katz Index, PSMS); psychiatric (GDS, Cornell Scale, CES-D)
Laboratory and other:
CBC, Chemistry panel, TSH, Vitamin B ₁₂ level, Syphilis serology, Urinalysis, ECG, CXR
As indicated:
CT or MRI (often needed), Neuropsychologic testing, EEG, CSF examination, Apo E

genotyping

ADAS-Cog, Alzheimer's Disease Assessment Scale—Cognition; Apo E, apolipoprotein E; CBC, complete blood count; CES-D, Center for Epidemiologic Studies—Depression Scale; CSF, cerebrospinal fluid; CT, computed tomography; CXR, chest x-ray; ECG, electrocardiogram; EEG, electroencephalogram; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PSMS, Physical Self Maintenance Scale; TSH, thyroid-stimulating hormone.

Appendix-1

Behavioral manifestations of subcortical vascular dementia caused by lesions interrupting prefrontal-subcortical circuits.

<u>Circuit lesions</u>	<u>Brian lesion location</u>	<u>Manifestations</u>
Dorso-lateral prefrontal	dorsolateral prefrontal cortex head of the caudate nucleus lacunar lesions in putamen or thalamus	Executive dysfunction, poor word list generation, decreased verbal fluency
Orbito-frontal-subcortical	Lateral orbitofrontal cortical territories Subcortical -- caudate, basal ganglia, thalamus or white matter loop links	Disinhibited behaviors, mania, obsessive-compulsive disorder
Medial-frontal (cingulate) cortex-subcortical	Medial frontal cortical territories Subcortical-	Apathy, Slowing of information processing, mood changes, or vascular depression

Modified from Cummings JL. Frontal-subcortical circuits and human behavior. Arch Neurol 1993;50:873–80

Appendix 2 -- THE MINI-MENTAL STATUS EXAMINATION

TEST	SCORE
Orientation: What is the month, day, date, year, season? Where are you, what floor, city, county and state? (score 1 point for each item correct)	10
Registration: state three items (ball, flag, tree) (score 1 point for each item that the patient registers without you having to repeat the words. You may repeat the words until the patient is able to register the words but do not give them credit. You must also tell the patient that he/she should memorize those words and that you will ask him/her to recall those words later).	3
Attention: Can you spell the word WORLD forwards, then backwards? Can you subtract 7 from 100, and keep subtracting 7? (100-93-86-79-72) (Do both items but give credit for best of the two performances).	5
Memory: Can you remember those three words I asked you to memorize? (Do not give clues or multiple choice).	3

Appendix 2 -- THE MINI-MENTAL STATUS EXAMINATION	
TEST	SCORE
Languages:	
Naming: Can you name (show) a pen and a watch?	2
Repetition: Can you repeat "No if's, and's, or but's"?	1
Comprehension: Can you take this piece of paper in your right hand, fold it in half, then put it on the floor? (score 1 point for each item done correctly)	3
Reading: Read and obey, "CLOSE YOUR EYES"	1
Writing: Can you write a sentence?	1
Visuospatial: Have patient copy intersecting pentagons	1
TOTAL	30

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