Micro Vascular Dementia
Andres G. Morales, D.O.
Objectives

• Differentiate the major features of vascular dementia compared to neurodegenerative dementias such as Alzheimer’s dementia.

• Understand the pathophysiology and mechanisms which lead to vascular dementia.

• Develop treatment / management strategies in the care of vascular dementia.
Subcortical ischemic disease is the most common etiology of the vascular dementias.

a. True
b. False
Which of the following risk factors is most closely associated with subcortical vascular cognitive impairment?

a. Hyperlipidemia  
b. Diabetes  
c. Hypertension  
d. Tobacco use
The prevalence of pure Alzheimer’s disease as a cause of dementia is lower than previously reported.

a. True
b. False
Definition and Statistics

- Vascular dementia (VaD) is the loss of cognitive functions of enough severity to interfere with ADL’s as a result of cerebrovascular disease, both hemorrhagic and ischemic or other mechanisms that cause circulatory collapse and ultimately injury to brain tissue.

- VaD is the second leading cause of dementia after Alzheimer’s disease accounting for >20% of cases.

- Tends to be more common in men.

- Most common in populations at risk for small-vessel ischemic disease: Hispanics, Blacks, Asian.
Historical Notes

• Thomas Willis (1672) first described elderly patients with a dementia seen after stroke.

• Hemorrhage was thought to be the etiology of stroke until Abercrombie (1828) demonstrated arterial occlusion and infarction as etiologies of stroke.

• Kahlbaum (1863) described a syndrome of progressive dementia after stroke.

• Between 1894 - 1910, Kraepelin, Binswanger and Alzheimer identified dementia as due from either diffuse brain dysfunction or from focal brain disease.
Historical Notes

- Arteriosclerosis considered to be main cause of dementia

- Binswanger recognized a progressive dementia associated with subcortical vascular white matter lesions and focal neurological deficits.

- The term progressive subcortical vascular encephalopathy (PSVE) later known as Binswanger’s disease

- Binswanger’s disease was thought to be rare until the advent of better imaging techniques where developed in 1980’s and 90’s
Historical Notes

• Multi-infarct dementia was coined during the mid 20th century

• “Vascular dementia” came into favor when other mechanisms of vascular brain injury aside from infarction were identified

• AD by the 1980’s overshadowed VaD
AD vs VaD

- AD features primarily amnesic, language disorders, aphasia, agnosia, apraxia
- VaD memory loss less prominent, frontal lobe dysfunctions more prominent such as mood, apathy, pseudobulbar features, gait disturbances, motor slowing, incontinence, behavior disorders and focal neurologic signs and executive dysfunction
Clinical Forms of Vascular Dementia

- Large-vessel dementia
- Small-vessel dementia
- Ischemic-hypoperfusive dementia
- Hemorrhagic dementia
Small-Vessel Dementia

- Subcortical ischemic vascular dementia (SIVD, SVD)
- Accounts for 50% or > of all ischemic brain injury
- The predominate areas affected are the fronto-cortical and subcortical pathways, subcortical gray matter
SIVD

- 15-25% over 65 years have silent infarcts
- 80% of the elderly have evidence of cerebrovascular disease
- Degree of white matter ischemic disease on imaging studies correlates with degree of cognitive impairment
There are three small vessel ischemic syndromes which encompass most SIVD:

- Lacunar State
- Strategic infarction
- Binswanger’s disease (white matter ischemic gliosis)
Lacunar State

• Clinical syndrome resulting from the presence of multiple brain lacunes

• Lacunes are small areas of ischemic necrosis and liquefaction < 15 mm diameter

• Occlusion of arterial lumen of small arterioles

• Typical locations: basal ganglia, internal capsule, thalamus, pons, corona radiata, centrum semiovale
Lacunar State

- History of repeated small strokes with transient motor deficits and minimal residual injury
- Other clinical features: sudden hemiparesis, dysarthria, not aphasia, apathy or other mood disorders, ataxia
Lacunar Infarcts

Fig 2. MRI at six years of age. Axial FLAIR and T2-weighted fast spin-echo, and sagittal T1-weighted post gadolinium images showing the appearance of cysts (perivascular lacunes).
Strategic Infarction

- This dementia syndrome is characterized by marked apathy, poor attention, impaired mental control, both retrograde and anterograde amnesia.

- Single strategically placed infarctions typically in the thalami, head of the caudate nucleus, genu of the internal capsule.
Lacunar Infarct
Binswanger’s Disease
(ischemic white matter gliosis)

- Slowly progressive dementia, typically long history of hypertension or other systemic vascular disease
- Gradual accumulation of focal neurologic signs, such as weakness, pyramidal signs, gait disturbance, urinary incontinence
- Neuropsychological changes: pseudobulbar palsy, apathy, depression, mood disturbances
- Ventriculomegaly due to central atrophy
White Matter Gliosis
White Matter Ischemic Disease
Figure. (A) On T1-weighted MRI, the white matter abnormalities are not well shown.

Valencia C et al. Neurology 2001;56:610-610
VaD Risk Factors

- Advancing age
- Isolated systolic hypertension
- Hypertension
- Tobacco smoking
- Diabetes
- Hyperlipidemia
- Atrial fibrillation
VaD Risk Factors

- Congestive heart failure
- Obstructive sleep apnea
- Orthostatic hypotension
- CABG surgery
- Major surgery in elderly
- Stroke
Pathophysiology of VaD

- White matter ischemic disease associated with both cognitive impairment and focal signs in otherwise normal appearing individuals
- Functional MRI demonstrates diminished cerebral perfusion in areas of white matter changes
- Functional MRI demonstrates an inverse relationship between degree of white matter gliosis and glucose metabolism
- Hypertension and smoking correlate with the degree of white matter disease
Pathophysiology of VaD

- Episodic hypotension, dysrhythmias and carotid sinus hypersensitivity in the face of diminished vascular reserve and poor vasoreactivity
- All the above lead ultimately to endothelial dysfunction
- Leads to increased water content in axons and loss of myelin
- Ependymal breakdown and transependymal diffusion develops
Pathophysiology of VaD

- Breakdown of blood-brain barrier with extravasation of plasma proteins
- Frank infarction in lacunar disease from arteriolar thrombosis and necrosis and inflammatory injury
- Hypertension also leads to hyaline necrosis with weakened endothelium and micro-bleeds
Diagnostic Criteria

- VaD diagnosed when a syndrome of dementia is noted concurrently with evidence of CVD
- No pathognomonic pathological lesions of vascular dementia (gliosis does not imply dementia)
- Diagnosis of exclusion
- Current office screening tools such as the MMSE and clock drawing test are inadequate
- CT or MR imaging is critical
Diagnostic Criteria

- Hachinski Ischemic Score
- Short bedside tool for determining between the two major types of dementia, Alzheimer’s vs Vascular
- 13 item assessment with score ranging from 0-18
- Score $\leq 4$ consistent with DAT
- Score $\geq 7$ consistent with VaD
- Sensitivity 89% and specificity of 89%
- **Not a test of dementia**
<table>
<thead>
<tr>
<th>Item No.</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abrupt onset</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Stepwise deterioration</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Fluctuating course</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Nocturnal confusion</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Preservation of personality</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Depression</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Somatic complaints</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Emotional incontinence</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>History of hypertension</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>History of stroke</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>Associated atherosclerosis</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>Focal neurological symptoms</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>Focal neurological signs</td>
<td>2</td>
</tr>
</tbody>
</table>
NINDS - AIREN criteria for the diagnosis of vascular dementia

I. The criteria for the clinical diagnosis of probable vascular dementia include all of the following:

1. **Dementia** defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferable established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.

*Exclusion criteria*: cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.

2. **Cerebrovascular disease**, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of not relevant CVD by brain imaging (CT or MRI) including *multiple large vessel infarcts* or a *single strategically placed infarct* (angular gyrus, thalamus, basal forebrain, or PCA orACA territories), as well as *multiple basal ganglia and white matter lacunes, or extensive periventricular white matter lesions, or combinations thereof*.

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 months following 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 vascular dementia include the following:

(a) Early presence of gait disturbance (small-step gait or marche a petits pas, or magnetic, apraxic-ataxic or parkinsonian gait); (b) history of unsteadiness and frequent, unprovoked falls; (c) early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease; (d) pseudobulbar palsy; and (e) personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

III. Features that make the diagnosis of vascular dementia uncertain or unlikely include (a) early onset of 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; (b) absence of focal neurological signs, other than cognitive disturbance; and (c) absence of cerebrovascular lesions on brain CT or MRI.

IV. Clinical diagnosis of possible vascular dementia may be made in the presence of dementia (section I-1) with focal neurologic signs in patients in whom brain imaging studies to confirm definite CVD are missing; or in the absence of clear temporal relationship between dementia and stroke; or in patients with subtle onset and variable course (plateau or improvement) of cognitive deficits and evidence of relevant CVD.

V. Criteria for diagnosis of definite vascular dementia are (a) clinical criteria for probable vascular dementia; (b) histopathologic evidence of CVD obtained from biopsy or autopsy; (c) absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age; and (d) absence of other clinical or pathological disorder capable of producing dementia.

VI. Classification of vascular dementia for research purposes may be made on the basis of clinical, radiologic, and neuropathologic features, for subcategories or defined conditions such as cortical vascular dementia, subcortical vascular dementia, BD, and thalamic dementia.

The term "AD with CVD" should be reserved to classify patients fulfilling the clinical criteria for possible AD and who also present clinical or brain imaging evidence of relevant CVD. Traditionally, these patients have been included with VaD in epidemiologic studies. The term "mixed dementia," used hitherto, should be avoided.

adapted from The National Institute of Neurological Disorders and Stroke
Treatment and Management of VaD

- Primary treatment focuses on the underlying causes of VaD: hypertension, diabetes, tobacco use, dyslipedemia, atrial fibrillation, stroke
- Depression (some concern regarding TCA’s)
- Stabilization of behavior disorders such as aggression, anger, social disinhibition (valproic acid, lamotrigine, carbamazepine, benzodiazepines)
Treatment and Management of VaD

- Avoid antipsychotics
- Pravastatin improves vasomotor reactivity but has not shown to impact the development of white matter ischemic disease
- Efficacy and safety of the calcium antagonist nimodapine vs placebo after 52 weeks found no significant difference in cognition after treatment
Erkijuntti and colleagues (2002) demonstrated a statistically significant benefit in galantamine vs placebo.

Wilkinson and colleagues (2003) also found similar benefits with donepezil vs placebo.

Pratt (2002) largest trial using donepezil vs placebo demonstrated significant benefits over placebo.

Eisai Co. Ltd. reported in 2006, 11 unexpected deaths in patients taking Aricept during the phase III trial in vascular dementia. Cause is unknown.

Cholinesterase inhibitors have been approved for VaD in Asia but not the U.S.
Treatment and Management of VaD

- Memantine demonstrated general benefits and reduction in caregiver burden (Winblad 1999)
- Orogozo et al (2002) some benefit in vascular dementia as well
- Memantine is not approved for the treatment of VaD
Prevention of VaD

• Several longitudinal community-based studies have provided evidence that identification and control of risk factors in midlife reduces risk of cognitive impairment:
  
  • Framingham Heart Study demonstrated declines in cognitive function based on magnitude of hypertension
  
  • Rotterdam Scan Study: hypertension of 5 - 20 years duration was associated with increased white matter lesions
Prevention of VaD

• Honolulu Asia Aging Study: beginning 1965 for every 10 mm Hg increase in SBP there was a 7% increase risk of cognitive decline. In a follow-up study, for each year of antihypertensive tx, there was a reduction in risk of dementia

• Cardiovascular Health Study: control of cigarette smoking, lowering homocysteine and lipid lowering, reduced worsening of white matter gliosis
Prevention of VaD

- Systolic Hypertension in Europe trial: long-term antihypertensive therapy over 3.9 years reduced risk of dementia by 55%

- Perindopril Protection Against Recurrent Stroke (PROGRESS) patients with prior stroke or TIA randomized to perindopril +/- indapamide vs placebo demonstrated 19% RR reduction in cognitive decline and 43% reduction in new white matter lesions
Treatment Statistics of Risk Factors

- Only 70% of Americans with HTN are aware, 60% get treated and 34% are controlled successfully.

- Patients with atrial fibrillation: < 60% of those receiving treatment are on therapeutic doses.

- Between 2007-2009 16% of diagnosed diabetics were not receiving treatment.
Subcortical ischemic disease is the most common etiology of the vascular dementias.

a. True
b. False
Which of the following risk factors is most closely associated with subcortical vascular cognitive impairment?

a. Hyperlipidemia
b. Diabetes
c. Hypertension
d. Tobacco use
The prevalence of pure Alzheimer’s disease as a cause of dementia is lower than previously reported.

a. True  
b. False
The use of the Folstein Mini Mental Status Examination as a tool for the diagnosis of subcortical vascular dementia is both highly sensitive and specific.

a. True
b. False