Vascular Contributions to Cognitive Impairment and Dementia: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

Philip B. Gorelick, Angelo Scuteri, Sandra E. Black, Charles DeCarli, Steven M. Greenberg, Costantino Iadecola, Lenore J. Launer, Stephane Laurent, Oscar L. Lopez, David Nyenhuis, Ronald C. Petersen, Julie A. Schneider, Christophe Tzourio, Donna K. Arnett, David A. Bennett, Helena C. Chui, Randall T. Higashida, Ruth Lindquist, Peter M. Nilsson, Gustavo C. Roman, Frank W. Sellke and Sudha Seshadri

• Summarizes current state of knowledge.
• Offers new diagnostic criteria.
• Provides recommendations for clinical care.
• Identifies priority areas for research.

Stroke. 2011; 42: 2672-2713
Existing Criteria

• ICD-10.
• DSM-IV.
• NINDS-AIREN.
• State of California Alzheimer’s Disease Diagnostic and Treatment Centers.
Limitations of Existing Criteria

• Dated, do not take into account newer concepts in cognitive impairment:
  – Improved classification of milder forms of impairment (MCI).
  – Significance of silent (“covert”) cerebrovascular disease, based on neuroimaging and neuropathology studies.

• Improvements in neuroimaging markers.

• Poor sensitivity.

• Poor reliability between criteria.
Poor agreement between criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>NINDS-AIREN</th>
<th>DSM-IV</th>
<th>California¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable VaD</td>
<td>9%</td>
<td>13%</td>
<td>25%</td>
</tr>
<tr>
<td>Possible VaD</td>
<td>2%</td>
<td>--</td>
<td>20%</td>
</tr>
<tr>
<td>Total any VaD</td>
<td>11%</td>
<td>13%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Heterogeneity of Diagnosis of VaD

Erkinjuntti, *NEJM* 1997;337:1667
2011 AHA/ASA Approach to VCI Diagnosis

• Determine if cognitive impairment is present.
• Determine if cerebrovascular disease is present.
• Determine if there is a relationship between the cognitive impairment and the cerebrovascular disease.
  – Probable vs. possible categories based on strength of evidence.
2011 AHA/ASA Criteria

- Vascular cognitive impairment (VCI) = vascular dementia (VaD) and vascular MCI (VaMCI).
VaMCI

• Recommends classification of VAMCI into 4 subtypes: amnestic single domain, amnestic multiple domain, non-amnestic single domain, non-amnestic multiple domain.

• Minimum 4 domains to test: executive/attention, memory, language and visuospatial. Impairment in at least 1 domain.\(^1\)

• IADL normal or mildly impaired, independent of motor or sensory deficits from stroke.

\(^1\)Hachinski et al. VCI harmonization standards. Stroe 2006;37:2220-2241
Probable VaMCI

1. There is cognitive impairment and imaging evidence of cerebrovascular disease and:
   
a. There is a clear temporal relationship between a vascular event (eg, clinical stroke) and onset of cognitive deficits, or

b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (eg, as in CADASIL).

2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.
Possible VaMCI

There is cognitive impairment and imaging evidence of cerebrovascular disease but:

1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (eg, silent infarcts, subcortical small-vessel disease) and onset of cognitive deficits.

2. There is insufficient information for the diagnosis of VaMCI (eg, clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).

3. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (eg, annual cognitive evaluations) before the clinical event that caused aphasia could be classified as having probable VaMCI.

4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as
   
   a. A history of other neurodegenerative disorders
   b. The presence of Alzheimer disease biology is confirmed by biomarkers
   c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.
Unstable VaMCI

• Subjects with the diagnosis of probable or possible VaMCI whose symptoms revert to normal should be classified as having “unstable VaMCI.”
Probable VaD

1. There is cognitive impairment and imaging evidence of cerebrovascular disease and:
   
   a. There is a clear temporal relationship between a vascular event (eg, clinical stroke) and onset of cognitive deficits, or
   
   b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (eg, as in CADASIL).

2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.
Possible VaD

There is cognitive impairment and imaging evidence of cerebrovascular disease but:

1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (eg, silent infarcts, subcortical small-vessel disease) and the cognitive impairment.

2. There is insufficient information for the diagnosis of VaD (eg, clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).

3. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (eg, annual cognitive evaluations) before the clinical event that caused aphasia could be classified as having probable VaD.

4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as
   a. A history of other neurodegenerative disorders
   b. The presence of Alzheimer disease biology is confirmed by biomarkers
   c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.
Comments

• Neuroimaging confirmation of CVD is necessary for diagnosis of “probable” VaD or VaMCI.

• Evidence of other neurodegenerative conditions moves certainty into “possible” category; however, no explicit criteria for mixed dementia.

• Cause of VCI not part of classification.
  – However, information on type of CVD needed for clinical management.
Challenges to Diagnosing VCI in Practice

• Determine if cognitive impairment is present.
  – Can be done.

• Determine if cerebrovascular disease is present.
  – Relatively straightforward when stroke is present
  – But are current neuroimaging markers of “covert” CVD good enough?

• Determine if there is a relationship between the cognitive impairment and the cerebrovascular disease.
  – But CVD extremely common; can we discriminate “benign” from “malignant”?
  – What about mixed disease?
Established Neuroimaging
Markers of VCI

- Infarcts
- White matter lesions
- Microbleeds
Microinfarcts: The Invisible Lesions

- Seen microscopically but not on gross pathological examination.

Stroke. 2011 Mar;42(3):722-7
# Prevalence of Microinfarcts

<table>
<thead>
<tr>
<th>Study name</th>
<th>N</th>
<th>Population</th>
<th>Prevalence of Microinfarcts</th>
<th>Adjusted Odds Ratio (OR) for Dementia (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Overall</td>
<td>Dementia</td>
</tr>
<tr>
<td>ACT</td>
<td>221</td>
<td>Washington State USA, randomly selected members of Group Health Cooperative</td>
<td>97/209</td>
<td>47/74</td>
</tr>
<tr>
<td>BLSA</td>
<td>179</td>
<td>Baltimore, USA community</td>
<td>39/179</td>
<td>34/89 ³</td>
</tr>
<tr>
<td>Bronx Studies</td>
<td>190</td>
<td>Bronx, USA community including nursing homes</td>
<td>30/190</td>
<td>20/131 ³</td>
</tr>
<tr>
<td>CC75C Study</td>
<td>213</td>
<td>Cambridge, UK, community through general practices</td>
<td>103/213</td>
<td>60/113</td>
</tr>
<tr>
<td>HAAS</td>
<td>285</td>
<td>Honolulu, USA Japanese-American men</td>
<td>55/285</td>
<td>35/118</td>
</tr>
<tr>
<td>Religious Orders</td>
<td>425</td>
<td>Older Catholic clergy from multiple U.S. centers</td>
<td>129/425</td>
<td>70/192</td>
</tr>
<tr>
<td>Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rush Study of Memory and Aging</td>
<td>148</td>
<td>Chicago, USA community mostly from retirement/seniors housing</td>
<td>35/148</td>
<td>14/51</td>
</tr>
<tr>
<td>Pooled</td>
<td>1649</td>
<td></td>
<td>488/1649</td>
<td>280.768</td>
</tr>
</tbody>
</table>
Microinfarcts and OR for Dementia
Community-based Studies

Odds Ratio for Dementia in Persons with Microinfarcts

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT\textsuperscript{6}</td>
<td>2.96 (1.64, 5.33)</td>
<td>15.47</td>
</tr>
<tr>
<td>BLSA\textsuperscript{34}</td>
<td>10.51 (3.87, 28.51)</td>
<td>10.31</td>
</tr>
<tr>
<td>Bronx Studies\textsuperscript{24}</td>
<td>0.88 (0.38, 2.83)</td>
<td>12.15</td>
</tr>
<tr>
<td>CC75C\textsuperscript{82}</td>
<td>1.50 (0.87, 2.58)</td>
<td>16.12</td>
</tr>
<tr>
<td>HAAS\textsuperscript{9}</td>
<td>3.10 (1.68, 5.71)</td>
<td>15.16</td>
</tr>
<tr>
<td>Religious Orders Study\textsuperscript{19}</td>
<td>1.69 (1.12, 2.57)</td>
<td>17.88</td>
</tr>
<tr>
<td>Rush Study of Memory and Aging\textsuperscript{17}</td>
<td>1.37 (0.63, 2.99)</td>
<td>12.90</td>
</tr>
<tr>
<td>Overall (I-squared=70.8%, p=0.002)</td>
<td>2.15 (1.38, 3.37)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
Established Neuroimaging Markers of VCI

- Microinfarcts
- Infarcts
- White matter lesions
- Microbleeds
Is VCI present?

What is the mechanism?

- Multi-infarct
- Strategic infarct
- White matter lesions

What cerebrovascular diseases are present?

- Identify and treat vascular disease and vascular risk factors
- Improve neurotransmitter function with acetylcholinesterase inhibitors
- Treat behavioral and other complications
- Caregiver and social support
VCI
Mechanism

Multi-infarct dementia

Strategic infarcts

White matter lesions

Etiology

Large artery atherosclerosis
Cardioembolism
Lacunar infarction
Hypoperfusion
Miscellaneous ischemic causes
Hemorrhage (subdural, intraparenchymal, subarachnoid)

Arterioloclerosis (age, hypertension)
Cerebral amyloid angiopathy
CADASIL
Fabry’s disease
Homocysteine-related
Strategic Infarct Dementia

Other proposed locations: genu of the internal capsule, corpus callosum, mesial temporal lobe
• Regions where white matter lesion involvement correlates with worse test performance are shown in the red-to-yellow scale.

• Testing done in 145 research subjects: 40 normal cognition, 94 MCI, 11 mild AD.

What About Mixed Disease?

• Not explicitly covered by either AD or VCI criteria.

• Are relationships between CVD and cognition the same or different in the presence or absence of other pathologies such as AD?

• Does pure subcortical ischemic dementia really exist?
**Final Neuropathology Diagnosis**

- Alzheimer's + CVD: 38%
- Pure Alzheimer's: 30%
- Pure Vascular Dementia: 12%
- Lewy Bodies: 12%
- Unclear: 8%

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**Clinical Diagnosis**

- Alzheimer's + CVD: 27%
- Pure Alzheimer's: 47%
- Pure Vascular Dementia: 9%
- Lewy Bodies: 3%
- Other: 14%

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Summary of Challenges and Areas for Future Research

• New criteria: need to determine reliability and accuracy.

• Microinfarcts may be most clinically relevant lesion but are “invisible”: need to identify them, or highly correlated markers, in life.

• Refine use of existing biomarkers by incorporating information on lesion location and severity; large datasets will be needed.

• Mixed disease is common: need to develop comprehensive biomarker profiles included CVD and AD markers.
Thank you