Vascular Cognitive Impairment

From Theory to Practice

Benjamin Lam MD FRCPC
Sunnybrook Health Science Centre

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Outline

1. Imaging primer
2. Vascular cognitive impairment (VCI) biology and definitions
3. Assessing VCI
4. Treating VCI
Imaging Primer

CT Scans
General notes

- CT scans are **quick** (seconds to minutes), relatively “**inexpensive**” ($250), and **widely available**

- Useful in the early detection of stroke
- Useful to rule out other pathologies (e.g. tumour)
Anatomy and Landmarks
Early Stroke Pathology
VCI

Biology and Definitions
VCI: It’s many causes...

Cardiovascular Risk Factors
- Hypertension
- Diabetes
- Genetics
- Hypercholesterolemia
- Heart Disease

Damage to Cerebral Vasculature

Multiple Distinct Pathologies
- Large Vessel Infarcts
  - Strategic Single Infarcts
  - Multi-infarct Dementia
- Small Vessel Infarcts
  - Multiple Lacunae
  - Binswanger’s /CADASIL
- Hemorrhage
  - Chronic SDH
  - SAH
  - ICH
- Hypoperfusion
  - Global (e.g., cardiac arrest)
  - Hypotension

Final Common Pathway
- Damage to critical cortical and subcortical structures
- Damage/interruption of subcortical circuits and projections

↓ Cholinergic transmission

VCI/VaD

Erkinjuntti. CNS Drugs. 1999.

Courtesy of S.E. Black, SHSC UT
Vascular Cognitive Impairment (VCI): Its many forms...

- Vascular Cognitive Impairment, No Dementia (VCIND) – “vascular MCI”

- Vascular Dementia
  - Several subtypes:
    - multi-infarct dementia (MID)
    - single strategic infarct
    - subcortical ischemic vascular dementia (SIVD)

- Mixed Alzheimer’s and Cerebrovascular Disease

Courtesy of S.E. Black, SHSC UT
# Clinical Features of Large and Small Vessel Disease

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Large vessel disease</th>
<th>Small vessel disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lesion location</strong></td>
<td>Cortical-subcortical</td>
<td>Subcortical (e.g. thalamus)</td>
</tr>
<tr>
<td><strong>Neurological signs</strong></td>
<td>Focal (i.e. sensory-motor)</td>
<td>None (40%) or mild</td>
</tr>
<tr>
<td><strong>Dementia-related Changes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td>Cortical dysfunction (aphasia, apraxia, agnosia, neglect, visual-spatial problems); memory loss</td>
<td>Executive Dysfunction Poor memory retrieval</td>
</tr>
<tr>
<td>Insight</td>
<td>Retained until late</td>
<td>Can be impaired</td>
</tr>
<tr>
<td>Affective/mood disturbances</td>
<td>Less common (except depression)</td>
<td>Apathy, anxiety, lability, irritability, low mood</td>
</tr>
</tbody>
</table>

*Cummings. *Dementia.* 1994*  

Courtesy of S.E. Black, SHSC UT
Components and Functions of the Frontal Lobes

Courtesy D. Stuss and S.E. Black
Summary of Mechanisms

- Damage to cognitive centers
- Damage to connection between cognitive centers
- Damage to “activators” of cognitive centers
Assessing VCI

The MoCA and the Hachinski Scale
The problem...

- There are two key challenges:
  1. Detecting VCI
     - Issue of sensitivity
     - MoCA
  2. Distinguishing VCI from its mimics
     - Issue of specificity
     - Hachinski Ischemic Score
Persons at Risk

- Have a high index of suspicion

- All patients with vascular risk factors and those with clinically evident stroke or transient ischemic attack should be considered at high risk for vascular cognitive impairment.

*Can Best Practice Stroke (6.3) CMAJ. 2008*
The Montreal Cognitive Assessment is considered more sensitive to cognitive impairment than the Mini Mental Status Exam in patients with vascular cognitive impairment [Evidence Level B]

Can Best Practice Stroke (6.3) CMAJ. 2008
Superiority of the MoCA

- VCI is characterized by more significant impairment of executive function (not adequately tested in MMSE)
- Memory impairment of VCI is usually more subtle (recall NINDS-AIREN criteria), and 3-word recall of MMSE is not sensitive to it

- High priority subsets of MoCA
  - Phonemic word list generation (F words)
  - 5 word registration and recall
  - 6 item orientation
Distinguishing from mimics: Hachinski Ischemic Score

Table 3.—Ischemic Score

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrupt onset</td>
<td>2</td>
</tr>
<tr>
<td>Stepwise deterioration</td>
<td>1</td>
</tr>
<tr>
<td>Fluctuating course</td>
<td>2</td>
</tr>
<tr>
<td>Nocturnal confusion</td>
<td>1</td>
</tr>
<tr>
<td>Relative preservation of personality</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>1</td>
</tr>
<tr>
<td>Emotional incontinence</td>
<td>1</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1</td>
</tr>
<tr>
<td>History of strokes</td>
<td>2</td>
</tr>
<tr>
<td>Evidence of associated atherosclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Focal neurological symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Focal neurological signs</td>
<td>2</td>
</tr>
</tbody>
</table>

Hachinski. Arch Neurol. 1975
Hachinski Score in Detail

- Abrupt onset 2
- Fluctuating course 2
- Stepwise deterioration 1
- Depression 1
- Emotional incontinence 1
- Relative preservation of personality 1
- Nocturnal confusion 1
- Somatic complaints 1

- History of strokes 2
- Focal neurological symptoms 2
- Focal neurological signs 2
- History of hypertension 1
- Evidence of associated atherosclerosis 1
Hachinski “Signs”

1. Sudden onset and fluctuating course
2. Stroke symptoms and history
3. Prominent mood disturbance
4. Preserved personality
Using the Score

- **Total score 0-18**
  - ≤4 : probably AD
  - 5-6 : mixed disease
  - ≥7 : probably VaD

- **Consider then...**
  - If someone has a stroke, they already have 6 points
  - If someone doesn’t have a history of stroke, but has abrupt onset with focal findings, they have 6 points
Treating VCI
General notes

- Treatment of cognition in VCI and post-stroke dementia is **interdisciplinary**

- **Pharmacologically:**
  - Secondary stroke prevention
  - SSRI
  - Cholinesterase inhibitors
  - NMDA antagonists
Treating Post-Stroke Depression

- Patients diagnosed with a depressive disorder should be given a trial of antidepressant medication, if no contraindication exists. No recommendation is made for the use of one class of antidepressants over another; however, side effect profiles suggest that selective serotonin reuptake inhibitors (SSRIs) may be favoured in this patient population [Evidence Level A]

Can Best Practice Stroke (6.2) CMAJ. 2008
Treating Post Stroke-VCI

- All **vascular risk factors should be managed aggressively to achieve optimal control** [Evidence Level A]

- **Cholinesterase inhibitors** should be considered for management of vascular cognitive impairment diagnosed using the NINDS–AIREN criteria [Evidence Level B]

*Can Best Practice Stroke (6.3) CMAJ. 2008*
Galantamine in AD+CVD or Probable VaD

Erkinjuntti et al. *Lancet* 2002

**Cognition/ADAS-Cog**

Mean (SE) change in ADAS-Cog from baseline

- Baseline
- 2 months
- 4 months
- 6 months

**Improvement**

***p < 0.001 vs baseline and placebo***

**Deterioration**

- Galantamine 24 mg/day
- Placebo

Courtesy of S.E. Black, SHSC UT
Erkinjuntti et al. *Lancet* 2002

Courtesy of S.E. Black, SHSC UT
TABLE 1. Demographics and Baseline Characteristics: ITT Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Memantine (n=147)</th>
<th>Placebo (n=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion female, n (%)</td>
<td>75 (51)</td>
<td>61 (43)</td>
</tr>
<tr>
<td>Age (mean±SD), years</td>
<td>76.6±6.5</td>
<td>76.1±6.86</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>146 (99.3)</td>
<td>141 (100)</td>
</tr>
<tr>
<td>Patients dependent on full-time care, n (%)</td>
<td>77 (52.4)</td>
<td>67 (47.5)</td>
</tr>
<tr>
<td>Time since onset of dementia (mean±SD), months</td>
<td>31.2±24.4</td>
<td>35.1±26.7</td>
</tr>
<tr>
<td>ADAS-cog (mean±SD)</td>
<td>20.6±9.55</td>
<td>21.5±8.71</td>
</tr>
<tr>
<td>MIS (mean±SD)</td>
<td>7.8±1.54</td>
<td>7.8±1.47</td>
</tr>
<tr>
<td>MMSE (mean±SD)</td>
<td>16.9±2.6</td>
<td>16.9±2.44</td>
</tr>
</tbody>
</table>

TABLE 2. Main Efficacy Results: ITT-OC Analysis With No Replacement of Missing Visits or Items

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Memantine (Mean±SD)</th>
<th>Placebo (Mean±SD)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIC-plus at week 28</td>
<td>3.82±1.39</td>
<td>4.11±1.48</td>
<td>0.284</td>
</tr>
<tr>
<td>ADAS-cog, week 28–week 0</td>
<td>−1.25±5.32</td>
<td>1.58±6.42</td>
<td>0.0016</td>
</tr>
<tr>
<td>MMSE total scores, week 28–week 0</td>
<td>1.75±3.83</td>
<td>0.52±4.07</td>
<td>0.0121</td>
</tr>
<tr>
<td>CGI-C (physician) at week 28</td>
<td>3.58±1.09</td>
<td>3.85±1.19</td>
<td>0.0838</td>
</tr>
<tr>
<td>CGI-C (caregiver) at week 28</td>
<td>3.52±1.26</td>
<td>3.82±1.31</td>
<td>0.0921</td>
</tr>
<tr>
<td>NIS/GER total score, week 28–week 0</td>
<td>2.73±11.67</td>
<td>3.26±12.95</td>
<td>0.0119</td>
</tr>
<tr>
<td>GBS total score, week 28–week 0</td>
<td>−0.36±15.38</td>
<td>3.38±16.34</td>
<td>0.1194</td>
</tr>
</tbody>
</table>

OC indicates observed cases. *A posteriori probability values based on Mann-Whitney Wilcoxon test (2-sided).
Memantine in Post-Stroke Cognition

Changes in ADAS-cog.

Supplemental
Conclusions

- VCI is a heterogeneous disease with varied causes and presentations
- Imaging and clinical features combine to permit for the detection of VCI and aid in distinguishing it from other causes of dementia
- Assessment for VCI must be done early and often
- While limited, cholinesterase inhibitor, NMDA antagonist, and SSRI therapy may be useful adjuncts to a comprehensive interdisciplinary treatment plan in post-stroke cognitive impairment
Fin
Supplemental Slides
VCI Risk Factors

- age > 65
- hypertension
- hyperlipidemia
- diabetes
- clinical stroke
- neuroimaging findings of covert stroke or white matter disease
- damage to other target organs
- cognitive or functional changes that are clinically evident or reported during history-taking.

Can Best Practice Stroke (6.3) CMAJ. 2008
VCI Post-Stroke Screening

- arousal
- alertness and attention
- orientation
- memory
- language
- agnosia,
- visual-spatial/perceptual function

- praxis
- Executive functions
  - Insight
  - Judgment
  - social cognition
  - problem-solving
  - abstract reasoning
  - Initiation
  - planning
  - organization [Evidence Level C]

Supplemental: Can Best Practice Stroke (6.3) CMAJ. 2008
VCI versus AD

The Hachinski Score
The Hachinski score

- Introduced in 1975 as a derivation of studies into hemispheric and regional blood flow in “degenerative” versus VaD-multi-infarct type.

- Degenerative disease shows relatively preserved blood flow, VaD patients showed reduced flow.
Pathology in the Hachinski Study

- Multi-infarct: atherosclerosis and multiple small infarcts

- Degenerative: senile plaques (amyloid-β), neurofibrillary tangles (hyperphosphorylated MAPT)
SSRI in Post Stroke Depression
The SSRI Question

- Routine use of prophylactic antidepressants is not recommended in post-stroke patients [Evidence Level A]

However...

Escitalopram and Problem-Solving Therapy for Prevention of Poststroke Depression
A Randomized Controlled Trial

- Context: Depression occurs in more than half of patients who have experienced a stroke. Poststroke depression has been shown in numerous studies to be associated with both impaired recovery in activities of daily living and increased mortality. Prevention of depression thus represents a potentially important goal.

- Objective: To determine whether treatment with escitalopram or problem-solving therapy over the first year following acute stroke will decrease the number of depression cases that develop compared with placebo medication.

- Design, Setting, and Participants: A multisite randomized controlled trial for prevention of depression among 176 nondepressed patients was conducted within 3 months following acute stroke from July 9, 2003, to October 1, 2007. The 12-month trial included 3 groups: a double-blind placebo-controlled comparison of escitalopram (n=59),
Escitalopram Study

- Non-depressed stroke patients
- Patients who received placebo were significantly more likely to develop depression than individuals who received escitalopram
  - Placebo: 11 major and 2 minor cases of depression [22.4%]
  - Escitalopram: 3 major and 2 minor cases of depression [8.5%]
- adjusted hazard ratio [HR] 4.5; 95%confidence interval [CI], 2.4-8.2; \( p < 0.001 \)

There is fair evidence of small magnitude benefits for **galantamine** on cognition function and behaviour in mixed Alzheimer and cerebrovascular disease. Galantamine can be considered a treatment option for mixed Alzheimer and cerebrovascular disease [Evidence Level B]

There is fair evidence of small magnitude benefits for **donepezil** in cognitive and global outcomes, with less robust benefits on functional measures. Donepezil can be considered a treatment option for vascular dementia [Evidence Level B]
Memantine in Post-Stroke Cognition

- **288 patients** (80% of recruitment)
- **NINDS-AIREN criteria for VaD, MIS ≥ 5 of 6 months**

- 2 week “run-in” with placebo then:
  - 50% randomized to memantine 10mg BID (with standard 3 week titration)
  - 50% randomized to placebo
  - Total treatment time (excluding run-in) 28 weeks

- Assessment at 12 and 28 weeks

- Main outcomes – **ADAS-cog, MMSE, CIBIC-plus**