Cerebral Small Vessel Diseases: How To Recognize and Treat

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- Carlos Camara, Hugh Markus.
- Research team.
- Epidemiology.
- Vascular pathology.
- Clinical syndromes.
- Preventing stroke and dementia.
- Trial of remote ischemic conditioning.
Cerebral Small Vessel Disease (SVD)

Radiological Manifestations of SVD

<table>
<thead>
<tr>
<th>Recent small subcortical infarct</th>
<th>White matter hyperintensity</th>
<th>Lacune</th>
<th>Perivascular space</th>
<th>Cerebral microbleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example image</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Schematic</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image6" alt="Image" /></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Usual diameter¹</th>
<th>≤ 20 mm</th>
<th>variable</th>
<th>3-15 mm</th>
<th>≤ 2 mm</th>
<th>≤ 10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comment</td>
<td>best identified on DWI</td>
<td>located in white matter</td>
<td>usually have hyperintense rim</td>
<td>usually linear without hyperintense rim</td>
<td>detected on GRE seq., round or ovoid, blooming</td>
</tr>
<tr>
<td>DWI</td>
<td>↑</td>
<td>↔</td>
<td>↔ / (↓)</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>FLAIR</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>T2</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>T1</td>
<td>↓</td>
<td>↔ / (↓)</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>T2* / GRE</td>
<td>↔</td>
<td>↑</td>
<td>(↓ if haemorrhage)</td>
<td>↔</td>
<td>↓ ↓</td>
</tr>
</tbody>
</table>

Prevalence of Cerebral Small Vessel Disease on Magnetic Resonance Imaging in the General Population Without Dementia

<table>
<thead>
<tr>
<th>Age Decade</th>
<th>≥1 Infarct</th>
<th>≥2 Infarcts</th>
<th>Beginning Confluent or Confluent White Matter Hyperintensities on MRI</th>
<th>Microbleeds&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>50–59</td>
<td>5–8%</td>
<td>1–2%</td>
<td>1%</td>
<td>T2*-Weighted Gradient Recalled Echo (GRE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Susceptibility-Weighted Imaging (SWI)/High-Sensitivity Sequence</td>
</tr>
<tr>
<td>60–69</td>
<td>7–12%</td>
<td>2–3%</td>
<td>1–4%</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>12–23%</td>
<td>3–6%</td>
<td>6–14%</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>25–38%</td>
<td>6–9%</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

MRI = magnetic resonance imaging.
<sup>a</sup> Data are aggregated from multiple population-based studies.
<sup>b</sup> As measured using the Fazekas scale.<sup>13</sup>
<sup>c</sup> As can be seen from the table, susceptibility-weighted imaging (SWI) and other newer, high-sensitivity MRI sequences detect about twice as many microbleeds as older T2*-weighted gradient recalled echo (GRE) sequences.
# Prognosis of Persons with Small Vessel Disease

## Hazard of Future Clinical Events in Patients with MRI Markers of Vascular Brain Injury

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Stroke</th>
<th>Dementia</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain infarct</td>
<td>2.38 (1.87-3.04)</td>
<td>1.29 (1.02-1.65)</td>
<td>1.64 (1.40-1.91)</td>
</tr>
<tr>
<td>High WMH</td>
<td>2.45 (1.93-3.12)</td>
<td>1.84 (1.40-2.43)</td>
<td>2.00 (1.69-2.36)</td>
</tr>
<tr>
<td>Microbleeds</td>
<td>1.98 (1.55-2.53)</td>
<td>1.41 (0.90-2.21)</td>
<td>1.53 (1.31-1.80)</td>
</tr>
</tbody>
</table>

Meta-analysis of estimates adjusted for age, sex, and vascular risk factors.

Recommendations for radiological diagnosis (STRIVE).
Investigations.
Risk stratification for ischemic stroke.
Considerations for antithrombotic strategies in patient patients with microbleeds.
WMH of presumed vascular origin should be reported with the use of a validated visual rating scale such as the Fazekas scale for MRI.


Periventricular hyperintensity (PVH) was graded as:
0 = absence, 1 = “caps” or pencil-thin lining, 2 = smooth “halo,” 3 = irregular PVH extending into the deep white matter.

Separate deep white matter hyperintense signals (DWMH) were rated as
0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, 3 = large confluent areas.
Cerebral Small Vessel Pathology

Two main pathologies:

1. **Arteriolosclerosis**: caused by aging, hypertension and conventional vascular risk factors.

2. **Cerebral amyloid angiopathy**: caused by vascular beta-amyloid deposition.

3. **Others**
   - **Genetic**: CADASIL, CARASIL, others.
   - **Venous**: collagenosis.
   - **Arteritis**
   - **Embolism**
   - **Branch occlusive disease**

Two Main Types of Cerebral Small Vessel Disease

Risk Factors
- Age
- Hypertension
- Diabetes
- Smoking

Vascular Pathology
- Arteriolosclerotic Small Vessel Disease
  - Small Subcortical Ischemic Stroke/TIA
  - Spontaneous Intracerebral Hemorrhage

Clinical-Radiological-Pathological Syndromes
- Cerebral Amyloid Angiopathy
  - Spontaneous Lobar Intracerebral Hemorrhage
  - Sulcal Subarachnoid Hemorrhage
  - CAA-related Inflammation
  - Transient Focal Neurological Episodes

Lacunar Stroke
Primary ICH

Depression
Apathy
Others

Behaviour
Cognitive
Gait

SVD

1/3 Dementia Risk

Many Manifestations

Stroke
Slowness
Falls
Pathophysiology of Small Vessel Disease

LACUNAR STROKE
Lacunar Stroke Subtypes

- Isolated lacunar infarct
- Diffuse small vessel disease.
- Branch occlusive disease.
- Embolism.
- Cavitating white matter lacunes


Branch Occlusive Disease

Cavitating Lacunes


INTRACEREBRAL HEMORRHAGE AND CAA
- SVD causes primary ICH.
- Can be subtyped based on location: deep (basal ganglia, brainstem, subcortical white matter)
  - Different risk factors.
  - Different path correlates.
  - Different outcomes.

Conventional Treatment

- Acute (<4.5 hours) small subcortical infarct: tPA.
- Prevent recurrent ischemic stroke:
  - Blood pressure control.
  - Antithrombotic.
  - Statin.
- Prevent recurrent primary ICH:
  - Blood pressure control.
- CAA: no disease-modifying treatments.

Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke

Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial

<table>
<thead>
<tr>
<th>Stroke</th>
<th>Higher-target group (n=1519)</th>
<th>Lower-target group (n=1501)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>Rate (% per patient-year)</td>
<td>Number of patients</td>
<td>Rate (% per patient-year)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All stroke</td>
<td>152</td>
<td>2.77%</td>
<td>125</td>
<td>2.25%</td>
</tr>
<tr>
<td>Ischaemic stroke or unknown</td>
<td>131</td>
<td>2.4%</td>
<td>112</td>
<td>2.0%</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>21*</td>
<td>0.38%</td>
<td>13†</td>
<td>0.23%</td>
</tr>
<tr>
<td>Intracerebral</td>
<td>16</td>
<td>0.29%</td>
<td>6</td>
<td>0.11%</td>
</tr>
</tbody>
</table>

No benefit
Past Failures in Vascular Cognitive Impairment

Trials for Cerebral Small Vessel Disease

- Systematic review of Pubmed and Clinicaltrials.gov identified 1 additional phase 3 and 23 phase 2 trials targeting SVD progression or lacunar infarct prevention; 17 still ongoing.

- Interventions:
  - Vasodilators: cilostazol, isosorbide dinitrate.
  - Antihypertensives: telmisartan, tadalafil, amlodipine, losartan, atenolol.
  - Other drugs: allopurinol, DL-3-n-butylphthalide.
  - Systolic blood pressure lowering.
  - Aerobic exercise, resistance training, dancing.
  - Remote ischemic conditioning.

Trial of Remote Ischemic Pre-Conditioning in Vascular Cognitive Impairment (TRIC-VCI)

Clinicaltrials.gov NCT 04109963
Over 3 decades ago, investigators found that experimentally inducing short-lasting IR (for periods that do not result in tissue injury) before an actual injurious event, reduces the subsequent injury. This is known as Ischemic Preconditioning (IP).

The rationale is that these short periods of IR induce an endogenous protective environment, consisting of humoral and neuronal-mediated responses.

Remote ischemic preconditioning

- Neural:
  - kATP
  - A1R
  - mTOR
  - ↓ Inflammation
  - Antioxidant
  - HIF1α
  - NO
  - ERK
  - AKT

- Humoral:

Remote Preconditioning

Tolerance to Ischemia

In addition to early phase effects, there are longer term effects resulting from changes in gene expression and protein synthesis.

- Metabolic
- Energy
- Blood-flow
- Inflammatory
- Oxidative
- Genes

### Human Trials

#### Pre-procedural
- Cardiac surgery
- PCI/CABG
- AAA repair
- Carotid stent

#### Protection against recurrent event
- TIA/stroke due to intracranial atherosclerosis
- Cerebral small vessel disease and MCI

### Recent systematic reviews:
Safety and Tolerability

- Thousands of patients have undergone RIC
- No major AE have been reported.
- Populations have included severely ill patients (transplant recipients, major vascular surgery...).
- Frequently used exclusions: Prior history of vascular, soft tissue or orthopedic injury; history of peripheral vascular disease involving the arms.
- Patients on anticoagulants often excluded.
<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Range</th>
<th>n/N (Pooled), % of patients (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local petechiae</td>
<td>0 to 9.5%</td>
<td>11/201, 5.5% (2.3-8.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meng 2012, Meng 2015, Nicholson 2015, Zhao 2017, Zhao 2018</td>
</tr>
<tr>
<td>Intolerable discomfort</td>
<td>0 to 7.7%</td>
<td>1/337, 0.3% (0-0.9%)</td>
</tr>
<tr>
<td>Thrombophlebitis or DVT</td>
<td>0%</td>
<td>0/533</td>
</tr>
<tr>
<td>Limb ischemia</td>
<td>0%</td>
<td>0/533</td>
</tr>
</tbody>
</table>
3/5 subjects with MRI every week for 16 weeks had new small infarcts.

Bilateral carotid occlusion model (BCAS)

Bilateral hind limb RIC once daily for 1 month or 4 months

Results:
- Increased CBF
- Increased angiogenesis
- Decreased white matter damage

TRIC-VCI Protocol

Visit | Screening | Randomization | Phone | Phone | End Treatment | End
---|---|---|---|---|---|---
Time | -14 | 0 | 2±1 | 15±2 | 30±2 | 90±2

Measurements | Eligibility | Feasibility | Safety/tolerability | Efficacy | Feasibility | Safety/tolerability | Efficacy | Efficacy

4 cycles RIPC, single arm, once daily | 4 cycles RIPC, both arms, once daily | 4 cycles RIPC, single arm, once daily | Run-in | Treatment | No treatment; Sustainability | Phase
<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Operationalized as:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence of cerebral small vessel disease on CT or MRI</td>
<td>Evidence of either:</td>
</tr>
<tr>
<td></td>
<td>1. Beginning confluent WMH (ARWMC grade 2) on any slice on CT or MRI OR</td>
</tr>
<tr>
<td></td>
<td>2. Two or more supratentorial subcortical infarcts</td>
</tr>
<tr>
<td>2. Objective evidence of cognitive impairment</td>
<td>MoCA score ≤24</td>
</tr>
<tr>
<td>3. Concern on the part of the patient, caregiver, or clinician that there has been a decline from previous level of cognitive functioning,</td>
<td>AD8 questionnaire (administered to informant) with 2 or more positive responses, or clinical judgement based on self report of participant or observations by examiner</td>
</tr>
<tr>
<td>4. Independent with basic daily activities of living</td>
<td>Bristol Activities of Daily Living Scale response a) for questions 2, 4, 5, 6, 7, 8, 9, and 14.</td>
</tr>
</tbody>
</table>
• Non-commercial device sold by Seagull Company, Denmark.
• Blood pressure measurement, programmable to apply cycles of cuff inflation and deflation.
• Plan: 4 cycles of 5 minutes cuff inflation to 35 mmHg above systolic BP followed by 5 minutes deflation.
Primary Outcome

• Proportion completing ≥80% of the assigned sessions.
# Safety and Tolerability Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tolerability</th>
<th>Drop out rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Compliance</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>Arm injury</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain (visual analog scale)</td>
<td></td>
</tr>
</tbody>
</table>

![Visual Analog Scale Diagram]
## Secondary Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in cerebral blood flow (ASL MRI)</td>
</tr>
<tr>
<td>Change in MRI WMH volume</td>
</tr>
<tr>
<td>Change in MRI DTI PSMD</td>
</tr>
<tr>
<td>Change in Montreal Cognitive Assessment</td>
</tr>
<tr>
<td>Change in Trail Making A and B</td>
</tr>
<tr>
<td>Change in Neuropsychiatric symptoms (Mild Behavioural Impairment Tracking Tool)</td>
</tr>
<tr>
<td>Change in activities of daily living (Bristol scale)</td>
</tr>
</tbody>
</table>
MRI Biomarkers

- WMH Growth
- FLAIR
- Cerebral blood flow
- ASL MRI
- White Matter Disruption
- DTI Peak Skeletonized
- Mean Diffusivity
Thank You

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