Silent Cerebral Strokes: Clinical Outcomes and Management

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Overview

• What is silent CVD?
• Prevalence of silent CVD in AD
• Cognitive and Clinical Outcomes
• Management Perspectives
Case Discussion

- 62 year old Male/Right handed/Engineer
- Stroke at age 58-no residual deficits
- Wife noticed that patient has been forgetful for 1 year
  - Insidious onset and progressive
  - Misplacing his watch/documents
  - More repetitive
- MMSE-23/30
- CT brain-no focal lesions
- Diagnosis-Mild AD
Case Discussion

• Further History
  – Colleagues noticed that at work, he is staying back longer to finish his work
  – Ordered excessive supply of equipment
  – More withdrawn and quiet
  – 2 near falls over last 3 months

• Neurological Examination
  – Brisk deep tendon reflexes
  – Broad based cautious gait

• MOCA-19/30
Case Discussion

- MRI BRAIN

- Diagnosis?
  - AD
  - VaD
  - AD+CVD
AD or AD+CVD?

• Why differentiate?
• Prognosis
  – Clinical progression
  – Clinical Strokes
  – Mortality
• Management
  – Cognitive Enhancers
  – Vascular risk factors
  – Anti-platelets/Statins
  – Tocotrienols
Vascular Cognitive Impairment (VCI)

- Cognitive difficulties that are “caused by” or “associated with” cerebrovascular factors

- Includes spectrum of cognitive deficits ranging from mild impairment to established dementia

- Clinical spectrum
  - Vascular CIND (Cognitive Impairment No Dementia)
  - Vascular Dementia
  - Mixed Dementia (AD + Vascular)
Cerebrovascular disease and Cognitive disorders

**Clinical Criteria**
- Acute Onset
- Stepwise Decline
- Executive Impairment
- Working Memory Impairment
- Focal neurological Deficits
- Apathy & Depression
- Vascular Risk factors

**Neuroimaging Criteria**
- Acute Infarcts
  - Lacunar/Strategic/Cortical
- White Matter Hyperintensity
- Cerebral Microhemorrhage
- Chronic lacunes

**Pathological Criteria**
- Small vessel thrombosis
- Infarction/microinfarction
- Venous collagenosis

- Is clinical criteria alone sufficient?
- Is a combination of criteria required?
- How much of each is required?
- Pure versus mixed dementia?
Model for Vascular Cognitive Impairment

Vascular Risk factors (VRF)

Cerebrovascular disease (CVD)
- Small vessel
- Large Vessel

Vascular Brain injury (VBI)

Vascular Cognitive impairment
- VaD
- Mixed AD/VaD

MCI and Dementia related to AD pathophysiological process
- Amyloid
- Tau

AD + VRF

AD + CVD

AD + VBI

Higher resolution structural scans-microinfarcts
- Functional Imaging-cerebral connectivity deficits
Global Dementia Prevalence

Dementia is a major and growing problem in Asia

Nature, 2011
AD and VaD in Asia

Crude mean rate of Alzheimer's disease (AD) and vascular dementia (VD) in each region, in elderly aged 65 years and older.

Lopes et al, 2000
Types of Cerebrovascular Disease

Large Vessel strokes vs. small vessel strokes

ATHEROSECURSOSIS

ARTERIOLOBOSCLEROSIS
Neuroimaging Findings in CVD

- Multi-Infarct Dementia
- Strategic Infarct Dementia
- White Matter Disease
- White Matter Disease with Lacunes

- Large Vessel Cerebrovascular Disease
- Small Vessel Cerebrovascular Disease
- Strategic Infarcts
Components of Silent CVD

- **White Matter Hyperintensity**
  - non-homogenous hyperintensity on T2 or FLAIR with ill defined margins

- **Chronic Lacunes**
  - rounded or ovoid lesions, <15mm in diameter, of CSF signal intensity on T2 and FLAIR, generally with a hyperintense rim on FLAIR and no increased signal on DWI

- **Microhemorrhages**
  - Small <5 mm, homogeneous, round foci of low signal intensity on gradient echo images
Grading of WMH

- Fazekas Scale
  - Grade 1, 2, 3
  - Modified Fazekas, 0-12
  - Periventricular WMH
  - Deep Subcortical WMH

- Age Related White Matter Change Scale
  - 5 brain regions
  - 0-30 points
  - Longitudinal progression

- Volumetric measurements

Fazekas et al, 1987; Wahlund LO et al, 2001
Grading of Microhemorrhages

• Microbleed Anatomical Rating Scale (MARS)

Gregoire SM et al, 2009
Clinical relevance of WMH

• Pathological studies
  – correspond to areas of myelin loss and small vessel thrombosis (incomplete infarction)
• Strong association with hypertension
• Cognition Association
  – Impaired processing speed
  – Dysexecutive syndrome
  – Behavioural changes- apathy, depression

Gouw AA, 2011; Smith EE, 2008
White Matter Hyperintensity as a marker of small vessel strokes

- MRI WMH is a reliable surrogate marker for small vessel CVD
- Pathological studies have demonstrated a definite relationship between WMH and arteriolosclerosis

Deniz EL et al, 2013
Acute infarcts progress to WMH

- 5 patients with WMH underwent MRI weekly for 16 consecutive weeks.
- Tiny lesions arising de novo in the cerebral white matter. These lesions were clinically silent but had features of acute ischemic stroke.
- With time, the characteristics of these lesions approached those of pre-existing leukoaraiosis.
- Suggestion that tiny silent acute infarcts are a cause of WMH

Baseline WMH

Conklin J, 2014
Clinical Relevance of Microhemorrhages

- Etiology of microhemorrhage differs according to their location.
  - mH with a deep location are associated with hypertensive vasculopathy
  - mH in a lobar location are associated with cerebral amyloid angiopathy (CAA)

- Microhemorrhage are highly relevant in AD
  - Role of hypertension in pathogenesis
  - Amyloid deposition in parenchyma and in vessels (cerebral amyloid angiopathy)

- Microhemorrhage frequently associated with WMH and lacunes
- 5% prevalence in healthy individuals and 17% in memory clinic populations
- Associated with hypertension and diabetes
- Cognition
  - Frontal microhemorrhage have been associated with executive impairment independent of WMH or lacunes

Koennecke HC, 2006; Cordonnier C, 2007
Prevalence of Cerebrovascular Disease in AD

• Previous studies focused on large vessel strokes
• Small vessel strokes are more prevalent
  – Accounts for 70% of all VaD
• Particularly relevant to Asian populations
• Factors influencing prevalence of AD+ CVD
  – Type of CVD-small vessel vs large vessel
  – Diagnosis of AD-presence of biomarkers for AD
Dementia aetiology in the west

Jellinger, 2013
Prevalence of Mixed AD and Cerebrovascular Disease in an Asian population

Table 1 Demographic, clinical and MRI findings on CN, MCI, mild AD and moderate–severe AD subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>CN (n = 165)</th>
<th>MCI (n = 103)</th>
<th>Mild AD (n = 141)</th>
<th>Moderate–severe AD (n = 68)</th>
<th>Univariate P value</th>
<th>Multivariate P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>67.66 (6.23)</td>
<td>67.83 (6.66)</td>
<td>71.38 (8.63)</td>
<td>74.62 (8.47)</td>
<td>0.0001&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gender (males)</td>
<td>N (%)</td>
<td>77 (53.85)</td>
<td>41 (42.27)</td>
<td>62 (43.79)</td>
<td>23 (33.82)</td>
<td>0.040</td>
</tr>
<tr>
<td>Education (years)</td>
<td>Mean (SD)</td>
<td>11.80 (3.54)</td>
<td>9.35 (4.84)</td>
<td>6.57 (4.66)</td>
<td>4.21 (4.43)</td>
<td>0.0001&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>N (%)</td>
<td>25 (15.15)</td>
<td>13 (17.33)</td>
<td>39 (23.23)</td>
<td>13 (26.00)</td>
<td>0.004&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypertension</td>
<td>N (%)</td>
<td>95 (57.58)</td>
<td>36 (48.00)</td>
<td>81 (63.78)</td>
<td>29 (56.86)</td>
<td>0.185</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>N (%)</td>
<td>75 (49.34)</td>
<td>27 (38.57)</td>
<td>78 (64.46)</td>
<td>24 (48.98)</td>
<td>0.004&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mean (SD)</td>
<td>28.86 (0.76)</td>
<td>26.65 (0.48)</td>
<td>22.63 (3.88)</td>
<td>11.79 (3.19)</td>
<td>0.0001&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total MTA</td>
<td>Mean (SD)</td>
<td>3.42 (1.78)</td>
<td>3.41 (1.73)</td>
<td>4.28 (1.60)</td>
<td>6.02 (2.15)</td>
<td>&lt;0.0001&lt;sup&gt;b,g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total PVH</td>
<td>Mean (SD)</td>
<td>2.22 (1.32)</td>
<td>2.30 (1.34)</td>
<td>3.60 (1.97)</td>
<td>3.82 (1.93)</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total DSC</td>
<td>Mean (SD)</td>
<td>2.41 (1.67)</td>
<td>2.70 (2.00)</td>
<td>3.02 (1.26)</td>
<td>3.40 (1.50)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Total WMH</td>
<td>Mean (SD)</td>
<td>4.64 (2.60)</td>
<td>5.00 (2.84)</td>
<td>6.62 (2.93)</td>
<td>7.22 (3.10)</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Severe WMH</td>
<td>N (%)</td>
<td>11 (6.67)</td>
<td>10 (9.71)</td>
<td>40 (28.37)</td>
<td>27 (39.71)</td>
<td>&lt;0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

- High prevalence of vascular risk factors
- High prevalence of white matter disease in AD

Kandiah et al, 2014
Prevalence of Mixed AD and Cerebrovascular Disease in an Asian population

Relationship between White Matter Disease and Medial Temporal Atrophy at different stages of dementia

Kandiah et al, 2014
Severity of Silent Cerebral Ischemia increases with increasing severity of cognitive impairment

Kandiah et al, 2014
WMH is independently associated with BPSD in AD

- After correcting for age, baseline cognition and MTA, WMH remained significantly associated with a diagnosis of BPSD [odds ratio: 1.45 (1.14–1.85; p = 0.002)].
- With severe WMH, the association is significantly increased [odds ratio: 4.3 (1.3–12.5); p = 0.016]

![Bar graph showing mean PVH, DSC, and WMH scores in AD subjects with and without BPSD. Displayed p values are results of analysis by Wilcoxon-Mann-Whitney test.](image)

### Volumes of white matter disease and medial temporal atrophy among AD patients with and without BPSD

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 122)</th>
<th>BPSD (n = 45)</th>
<th>Non-BPSD (n = 77)</th>
<th>p value</th>
<th>Odds ratio (95% CI)</th>
<th>Adjusted p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PVH mean (SD)</td>
<td>4.66 (1.71)</td>
<td>5.44 (1.08)</td>
<td>4.21 (1.84)</td>
<td>0.0001</td>
<td>1.65 (1.09–2.52)</td>
<td>0.019</td>
</tr>
<tr>
<td>Total DSC mean (SD)</td>
<td>4.03 (1.80)</td>
<td>5.07 (1.32)</td>
<td>3.43 (1.77)</td>
<td>&lt;0.0001</td>
<td>1.89 (1.29–2.76)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total WMH mean (SD)</td>
<td>8.70 (3.21)</td>
<td>10.51 (2.15)</td>
<td>7.65 (3.26)</td>
<td>&lt;0.0001</td>
<td>1.45 (1.14–1.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Severe WMH (WMH ≥ 9)</td>
<td>72 (59.02)</td>
<td>37 (82.22)</td>
<td>35 (45.45)</td>
<td>&lt;0.001</td>
<td>4.03 (1.30–12.50)</td>
<td>0.016</td>
</tr>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total MTA mean (SD)</td>
<td>3.32 (2.19)</td>
<td>3.73 (2.17)</td>
<td>3.13 (2.19)</td>
<td>0.095</td>
<td>1.22 (0.95–1.56)</td>
<td>0.117</td>
</tr>
</tbody>
</table>

* Results from univariate analysis of neuroimaging data using t-test or Wilcoxon–Mann–Whitney test.

** Results from logistic regression analysis using BPSD status as the outcome variable, the corresponding white matter disease or MTA score as the predictor variable, and correcting for age and MMSE as potential confounders. White matter scores were additionally corrected for MTA, and vice versa.

Kandiah et al, 2013
WMH Independently Predicts progression from MCI to AD

- MCI patients with baseline MRI and 6-18 months of longitudinal follow-up were evaluated.
- Total of 171 MCI patients
- 19.4% annual risk of conversion
- MTA, periventricular WMH and deep subcortical WMH were significantly greater in the MCI-P cohort.
- WMH was found to predict MCI-P with an odds ratio of 7.69 (p = 0.03)
Pathophysiology: Role of CVD

- Direct neuronal loss following strokes
- Disruption to cerebral connections/pathways crucial for cognition
- Acceleration of amyloid and tau pathways resulting in more aggressive course of AD

*Image courtesy of Remedica Journals

Torakian F, 2014
Strokes and Ascending Cholinergic Pathways

- Periventricular white matter disease and lacunes can disrupt the ascending cholinergic pathways resulting in cholinergic deficiency and dementia
Frontal Subcortical Circuits

- Frontal-subcortical region often involved
- Disruption to fronto-striato-thalamo-frontal neural circuits

* Cummings 1993, McPherson and Cummings 1996*
Clinical Profile of AD + CVD

• Different from Pure Alzheimer’s Disease
• Common Presentation
  – Psychomotor Slowing
  – Dysexecutive Syndrome
  – Memory impairment
  – Apathy and depression
  – Gait difficulties
Dysexecutive Syndrome in Mixed AD

- Deficits in planning, sequencing, judgment
- Slowed processing speed due to deficit in sequencing
- Errors at work, home or social function due to deficit in planning
- Impaired judgment - wrong decisions
- Disruption to Frontal Subcortical Circuits
Memory Deficits in Mixed AD

- Early presentation
- Usually mild in nature
- Improves with cueing/reminders
  - Due to deficits in retrieval
  - Hippocampal dysfunction is mild
Gait Impairment in Mixed AD

• Frontal Disequilibrium Syndrome
  – Broad based
  – Hesitant, slow and shuffling
  – Fear of fall, poor postural control

• Related to lacunes and white matter disease in frontal lobe resulting in gait apraxia
Mood Changes in Mixed AD

• Early Apathy (not wanting to do anything)
• Withdrawn
• Depression
• Mood swings and lability
Cognitive Evaluation in Mixed AD

• Choose screening tests that evaluates both memory and executive function
• MMSE has limitations
• Montreal Cognitive Assessment
• Frontal Assessment Battery
• Clock Drawing test
AD vs. VaD: Cognitive Differences

Kandiah et al, 2009
WMH-Cognition Correlation

- 91 patients; mean age 64.9 years, mean education of 10.5 years
- Clinical and Neuropsychological Evaluation
- WMH volumetric quantification performed

Figure 1. Standardized performance on specific cognitive domains based on severity of WMH.

Kandiah et al, 2013
Management-Multidisciplinary

- Non-Pharmacological
  - Awareness
  - Cognitive Training

- Pharmacological
  - Anti-platelet/Anticoagulants
  - Optimization of vascular risk factors
  - Acetylcholine-esterase Inhibitors
  - Neuro-protectants
HTN and VaD

• Systematic review of 6 cohort studies:
  – positive association between hypertension and incident vascular dementia (AOR 1.59, 95% CI: 1.29-1.95)

• Studies from Asian populations:
  – Midlife hypertension was prospectively associated with risk for incident VaD
    • Honolulu Asia Aging Study (HAAS) (AOR 2.15, 95% CI: 1.25-3.71)
    • Hisayama (OR 3.09, 95% CI: 1.24-7.73)
  – Hisayama study (follow-up data), late-life hypertension was also associated with incident VaD
    • systolic hypertension OR 1.53, 95% CI: 1.16-2.01
    • diastolic hypertension OR 1.46, 95% CI: 1.11-1.90)

Yoshitake T, 1995; Sharp SI, 2011; Ninomiya T, 2011
Diabetes in late-life and incident vascular dementia

12 studies provided data on the association between diabetes in late-life and incident vascular dementia. The pooled RR was **2.39** (95% CI: 1.92-2.98)
Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score

• A risk score that predicts the likelihood of a middle aged person developing dementia within 20 years

• Risk of dementia
  – 1% for score of 0-5
  – 1.9% for score of 6-7
  – 4.2% for score of 8-9
  – 7.4% for score of 10-11
  – 16.4% for score of 12-15

• With a cut-off of 9 points
  – Sensitivity was 0.77
  – Specificity was 0.63
  – Negative predictive value was 0.98
Multidomain Intervention to prevent cognitive decline in the elderly

- Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)
- Randomized control trial with multidomain intervention
FINGER STUDY

- Methods
- Subjects 60–77 years old
- CAIDE Risk Score > 6
- Impairment in episodic memory (10 word list) or MMSE 20-26

Ngandu T, Lancet 2015
Intervention

• 2 year study
• Control group
  – regular health advice
• Intervention group
  – Four intervention components
    • Nutrition
    • Physical Exercise
    • Cognitive training
    • Vascular Risk Factor monitoring
Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.
Rivastigmine in Subcortical VaD over 22 months

Moretti, 2002
Role of Cognitive Enhancers in Mixed AD+CVD

Ng Kok Pin, Kandiah N, 2014
Tocotrienols and WMH

- 121 volunteers aged ≥35 years with cardiovascular risk factors and MRI-confirmed WMH
- Randomized to receive 200 mg mixed tocotrienols or placebo twice a day for 2 years.

Gopalan Y, 2014
Summary

• Silent CVD is prevalent
• Strongly associated with vascular risk factors
• Major Risk Factor for Strokes, Dementia and Mortality
• Treatment Trials with WMH as an endpoint are urgently required to reduce clinical strokes and dementia
THANK YOU
Probable AD: Core Clinical Criteria

A. **Insidious onset.** Symptoms have a gradual onset over months to years
B. Clear-cut history of worsening of cognition by report or observation; and
C. The initial and most prominent cognitive deficits are:
   - **Amnestic** presentation: most common
   - **Nonamnestic** presentation

Probable AD with evidence of the AD pathophysiological process

Biomarker supported diagnosis

- Biomarkers for amyloid-beta (Aβ) protein
  - low CSF Aβ42
  - positive PET amyloid imaging
- Biomarkers of neuronal degeneration
  - elevated CSF tau
  - decreased 18-FDG uptake on PET in temporo–parietal cortex
  - disproportionate atrophy on structural MRI in **medial temporal lobe**, and medial parietal cortex

McKhann et al, 2011
MOCA in Mixed AD

MONTREAL COGNITIVE ASSESSMENT (MOCA)

VISUOSPATIAL / EXECUTIVE

Copy cubes

Draw CLOCK (Ten past eleven)
(3 points)

NAME:

Education:

Date of birth:

Sex:

DATE:

POINTS

NAMING

Contour

Numbers

Hands

—/5

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

FACE VELVET CHURCH DAISY RED

1st trial

2nd trial

No points

ATTENTION

Read list of digits (1 digit/sec.)

Subject has to repeat them in the forward order

Subject has to repeat them in the backward order

Read list of letters. The subject must tap with his hand at each letter A. No points if 2 or more

Seizal 7 subtraction starting at 100

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

LANGUAGE

Repeat: I only know that John is the one to help today

The cat always hid under the couch when dogs were in the room

Fluency / Name maximum number of words in one minute that begin with the letter F

(N ≥ 11 words)

ABSTRACTION

Similarity between e.g. banana - orange - fruit

train - bicycle - watch - ruler

DELAYED RECALL

Has to recall words WITH NO DUE

FACE VELVET CHURCH DAISY RED

Points for UNCROSSED recall only

Optional

Multiple choice cue

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

26/30

TOTAL

Add 1 point if ≤ 12 yr edu
Vascular Contribution to Neurocognitive Syndrome

Pure AD

Multi-infarct VaD

Post-stroke Dementia

AD +SIVD