Vascular Cognitive Impairment

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No stock or equity interests
CT of 61 yo lawyer brought to ER a few weeks earlier confused, bumping into things.
Learning Objectives

1. Understand definitions, prevalence, subtypes and assessment of Vascular Cognitive Impairment

2. Appreciate role of co-morbid Cerebrovascular disease (CVD) and Alzheimer’s Disease (AD) in expressing dementia, and of shared vascular risk factors

3. Review management and use of cognitive enhancers in Vascular Dementia
The Boomer Bulge

2001

2011

2021
Common Covert Operatives that sabotage successful brain aging

- Alzheimer’s Disease
- Small Vessel Disease
- They must be recognized and their impact better understood to develop strategies to ameliorate and treat earlier and more effectively
- Also role for brain “reserve” (?size, synaptic complexity)
Definition of Dementia DSM IV (R)

• **Memory impairment** and at least one of: **Language difficulty; Apraxia; Visuospatial difficulty; Executive dysfunction**

• Impaired occupational or social functioning

• Decline from previous level of functioning

• DSM5-demotes memory, proposes to replace term dementia with **Major and Minor Neurocognitive Disorder**, depending on degree of autonomy in ADL’s

[www.dsm5.org](http://www.dsm5.org)
Diagnosis of Probable Alzheimer’s Disease: NINCDS – ADRDA Criteria

- Dementia clinically and by appropriate testing
- Deficits in two or more areas of cognition
- Progressive loss of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40-90
- Absence of other causes

McKhann et al. *Neurology*, 1984
Diagnosis of Probable Vascular Dementia: NINDS-AIREN Criteria

- Diagnosis of dementia
  - Cognitive decline (memory and two other domains)
  - Impaired functional abilities as a result of cognitive decline

- Evidence of cerebrovascular disease (CVD)
  - Focal neurological signs consistent with stroke
  - Brain CT or MRI required

- Relationship between dementia and CVD
  - Temporal association between the two – abrupt onset of dementia after CVD event
  - Sudden stepwise cognitive deterioration

Román et al. *Neurology*. 1993
Spectrum of Alzheimer’s Disease and Vascular Cognitive Impairment

AD, CVD, or both together account for approximately 80% of dementias


Spectrum of conditions including:
1. Vascular Cognitive Impairment-No Dementia (VCIND)
2. Vascular Dementia
   - Subtypes:
     • Multi-infarct dementia (MID)
     • Single strategic infarct
     • Subcortical ischemic vascular dementia (SIVD)
3. Mixed Alzheimer’s and Cerebrovascular Disease (CVD)

VCI: A Heterogeneous Disorder

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

↓ Cholinergic transmission

VCI/VaD

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Damage/interruption of subcortical circuits and projections
Vascular Cognitive Impairment

Harmonization Consensus Criteria
Hachinski et al Stroke 2006
60 and 30 Minute Protocols

Executive-Activation
Phonemic (FAS) Fluency
Semantic (Animal Naming) Fluency
WAIS-III Digit Symbol
Trailmaking Test

Language
Boston Naming Test – 15 item

Spatial
Complex Figure Copy

Memory
Hopkins or California Verbal Learning
(Immediate, Delayed, Recognition)
Complex Figure Delayed Recall
Incidental Learning: Boston Naming Test and Digit Symbol

Mood, Neuropsychiatric
CES-D
NPIQ

Other
IQCODE
MMSE

5 Minute Protocol
1. 5 word memory (registration, recall, recognition)
2. 6 item orientation
3. phonemic fluency

Montreal Cognitive Assessment (MoCA)
Hachinski et al Stroke 2006
Montreal Cognitive Assessment (MoCA)

- 30-point scale
- 10 minutes to administer
- One page
- All AD patients scored < 25
- Using cutoff < 25, MCI was discriminated from normals with
  - Sensitivity 80%
  - Specificity 91%

www.mocatest.org

Nasreddine et al. J AGS. 2005
Best Practice Recommendations: VCI & Dementia

Patients considered at high risk for cognitive and perceptual impairment are those with vascular risk factors such as hypertension, age > 65 year, hyperlipidemia, diabetes, clinical stroke, neuroimaging findings of covert stroke or white matter disease, damage to other target organs, and/or those patients with cognitive or functional changes that are clinically evident or reported during history taking.

CMAJ Dec 2, 2008
Overt Disease with Case examples
The Overt Disease: Post-Stroke Dementia

- By 3 months post-stroke, **65%** cognitively impaired
  - **26%-36%** meet criteria for dementia (vs **3%** in age-matched controls) \(^1,2\)
- Depressive symptoms post-stroke occur in **25-50%** \(^4,5\)
- Cognitive impairment increases long term dependence and is associated with higher mortality (**61%** vs **25%**) \(^1,2\)

72 yr old man presented with sudden onset confusion

Short term Memory Loss, anomia and executive dysfunction persisted
Multi-Infarct dementia

- **Mailman at age 39 suffered**
  - Right and left hemisphere strokes.
  - Bilateral carotid occlusions, R vertebral and basilar stenosis on angiography.

- **At age 61** seen in memory clinic for forgetfulness, anomia, difficulty with comprehension
  - MMSE 23/30
  - good function in activities of daily living but unable to work
  - hospital volunteer 3x/week, bingo, shopping
  - developed seizures, partially controlled on meds and died in status epilepticus at age 64
Final Diagnosis

- **Above**: MRI shows watershed strokes

- **Left**: Autopsy shows ischemic infarcts: neuronal loss and gliosis. No Alzheimer’s Disease
Subcortical Ischemic Vascular Disease – Cognitive Syndrome

EXECUTIVE DYSFUNCTION

• Impaired goal formulation, initiation, planning, organizing, sequencing, executing, set-shifting and maintenance, abstraction.

MEMORY DEFICIT (may be mild)

• Impaired recall, relative intact recognition, less severe forgetting, benefit from cues.
Clock Drawing
(Set hands to 10 after 11)

81 y.o. man
23 y.o.e.
Dx: AD w CVD
MMSE: 27/30

78 y.o. woman
12 y.o.e.
Dx: AD w CVD
MMSE: 25/30

75 y.o. woman
16 y.o.e.
Dx: VaD
MMSE: 26/30
78 y.o. woman, MMSE 30/30
SIVD – Early Clinical Features

- Gait disorder, imbalance
- Urinary frequency and incontinence
- Dysarthria, dysphagia
- Emotional incontinence
- Extrapyramidal signs (hypokinesia, rigidity)
- Depression and mood changes
The Covert Disease

Small vessel disease
Silent Stroke Prevalence

- 3 mm diameter lesions (hypointense on T1, hyperintense on T2) potentially relevant even if “silent”, ie covert infarcts

- Baseline MRI shows silent infarcts in 28% of seniors [3660 > 65, mean 75, in Cardiovascular Health Survey (CHS)] but frequency depends on age (12% seen in Framingham with mean age 62 yrs) (Longstreth et al, 1998; DeCarli et al Neurobiol Aging 2005)

- 10X as prevalent as overt infarcts (ie 15 million may have silent infarcts in the US)

- In the CVHS, in those with no baseline infarcts, 18 % showed them on rescan 5 years later (Longstreth et al 2002)
Small lacunes on T1 Weighted MRI

Focal Hyperintensity on Proton Density MRI
Prevalence is Linked to Age

Vermeer Lancet Neurol 2007
Covert is not benign

In > 1000 elderly aged 60-90 followed for 4 years in the Rotterdam Study, baseline silent infarcts on MRI meant:

- more rapid cognitive decline
- $2\times$ the risk of emergent dementia
- $5\times$ the risk of stroke
- $3\times$ stroke risk even after correcting for other vascular risk factors

Arteries and Arterioles
Small Vessel Disease

- Obliteration and occlusion
- Tortuosity, coiling
- Increased resistance
- Decreased autoregulation
- Endothelial changes
- BBB changes
- Perivascula changes
- CADASIL
Arteriolar Tortuosity

Thore et al Exp Neuro 2007

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White Matter Hyperintensities in Aging

- In Cardiovascular Health Study (N=3301 >65)
  - only 4.4% had no white matter lesions
  - 20% with extensive disease had poorer cognition, gait and dexterity \(^1\)

- Decreased psychomotor speed and global cognitive function with severe white matter disease seen in Rotterdam Study \(^2\)

1 Longstreth et al, 1996 2 DeGroot et al, 2000
Veins

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Confluent WMH, veins & sparing of u&long-fiber tracts

Vessel density = 31(w)/11(v) = 2.8

Gao et al, VASCOG 2009
Vascular Cognitive Impairment:

Overt and covert stroke disease often co-exist with Alzheimer’s Disease in the aging brain.
Common Risk Factors for Cognitive Impairment (AD and VaD)

Age
Midlife hypertension (Kivipelto et al, 2001; Launer et al, 2001)
Elevated cholesterol (Kivipelto et al, 2001)
APOE E4 (Slooter et al, 1998)
Diabetes (Arvanitikas et al, 2004)
Homocysteinemia (Seshradi et al, 2002)
Stroke and CAD
The Nun Study

• 102 sisters, aged 76 to 100 years, prospectively studied
• 61 met pathological criteria for AD, but only 57% met clinical criteria for dementia at autopsy
• Less AD pathology was needed for clinical dementia if infarcts present
• If AD and small strokes, 93% were demented
• Synergistic effect: if small vessel strokes, 20x risk of dementia (Snowdon et al JAMA 1997)
Community autopsy series: coexisting AD and CVD is common

In US population autopsy series:
- AD: 24-36%
- AD+CVD: 36-45%
- VaD: 3-13%
  (Lim et al, JAGS, 1999; Snowdon et al, JAMA, 1997)

In a British population (median age 85):
- 70% had AD and 78% had CVD
- Small vessel disease was most common (69%)
  (Neuropath Group, Lancet, 2001)
A. 148 Community Autopsies

Demented

![Pathologic Diagnoses Graph]

B. Not demented

![Pathologic Diagnoses Graph]
Vascular Cognitive Impairment

Co-morbidity: Case in Point
M.D. – 61 y.o. lawyer

- Became confused at work, bumping into objects
- Findings:
  - R hemianopsia & hemineglect
  - R sensory extinction
  - R pronator drift
  - Transcortical sensory aphasia (fluent speech), alexia & apraxia
- Angiography: no secondary cause
Gradient Echo

Microbleeds: Hemosiderin Deposits
M.D. - Course

- Unable to drive or work
- Persistent reading and calculation difficulties, but okay in other ADL’s
- Lost to follow-up and then reappeared 7 years later gradual onset memory loss (MMSE 16/30)
- Progressive decline in cognition and behaviour over 2 years with some initial response to donepezil
- Found without vital signs in nursing home 9 yrs post-hemorrhage
- Autopsy results: confirmed old hemorrhages, amyloid angiopathy and ?
Amyloid Angiopathy

Lobar Hemorrhage

Alzheimer’s Disease

Prada 2007

Vinters 2007

Chao 2006

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Pettersen et al
Arch Neur 2008

Pettersen et al
AnnNeur 2005
Trajectories of cholinergic pathways

(Selden et al. 1998)
Cholinergic Hyperintensity Pathway Scale (CHIPS)

Swartz et al, JStr CVD, 2002; Bocti et al, Stroke, 2008

Correlation of CHIPS and Dementia Rating Scale ($r^2=.12$, $p=.02$)
Galantamine: Cognitive Function: Subgroup Analysis

**Probable VaD**

<table>
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<th>Time (months)</th>
<th>Galantamine 24 mg/day (n=121)</th>
<th>Placebo (n=67)</th>
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*P* = .06 vs placebo

**Alzheimer’s disease with CVD**

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</table>

†*P* < .001 vs placebo and baseline

Galantamine Benefits Overall Global Functioning at 6 Months


![Graph showing Galantamine Benefits Overall Global Functioning at 6 Months.](image-url)
Donepezil: Cognitive Function
ADAS-cog (Prob/Poss. VaD)

Study week
LS Mean (±SE) Change From Baseline Score

Don 10 mg n= 380 370
Don 5 mg n= 387 372
Placebo n= 369 367

Don 10 mg: 334 309 298 380
Don 5 mg: 354 327 317 384
Placebo: 341 328 310 368

*P<0.001 versus placebo.

Donepezil: Functional Outcomes

IADL

LS Mean (±SE) Change From Baseline Score

Study week

Donepezil (10 mg/day)
Donepezil (5 mg/day)
Placebo

Don 10 mg n= 382 373 334 305 297 382
Don 5 mg n= 371 357 339 316 308 370
Placebo n= 362 359 334 322 306 361


*P<0.001; †P<0.01.
Summary

• Best Practice suggests screening for VCI in all phases of overt stroke disease, when silent stroke disease is uncovered, and even with vascular risk factors (including age)
• Standardized testing recommended—consider the harmonization criteria
• Small Vessel disease is ubiquitous in our aging population, often co-exists with AD and is not benign
• Executive functioning and speed of processing are important to assess if you suspect VCI
• Cholinesterase inhibitors are a potential (off-label) option for cognitive enhancement in VaD
Key Take Homes

- Post-stroke dementia can occur in 25% and VCI is common in elderly stroke patients.
- Mixed AD/CVD is likely the commonest substrate for dementia.
- A major goal for vascular medicine is risk factor control not just to prevent heart attack and stroke, but also dementia!
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