HOTCHKISS BRAIN INSTITUTE

UNIVERSITY OF CALGARY

VASCULAR COGNITIVE IMPAIRMENT:

Sweating the Small Stuff

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Disclosures

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Outline

- Background: dementia and the pathologies that cause dementia.
- Cerebral small vessel disease and dementia.
- Ongoing projects in our clinical research "lab".

Lifetime risk of dementia in women is 1 in 4 and in men is 1 in 6.

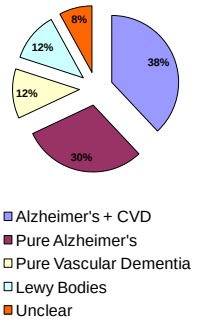
Alzheimer's disease (AD) is 7th leading cause of death in Canada.

(Lifetime risk of: breast cancer 1 in 8, prostate cancer 1 in 6, Parkinson's 1 in 15, epilepsy 1 in 26, multiple sclerosis 1 in 500.)

Seshadri, et al. Lancet Neurol 2007;6:1106-1114.

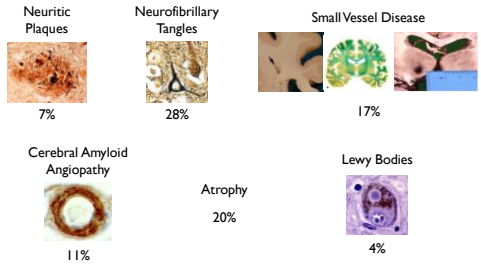
Statistics Canada (2008).

Neuropathologies of Dementia



Schneider et al, Neurology 2007:69:2197-2204.

Pathologies of Dementia

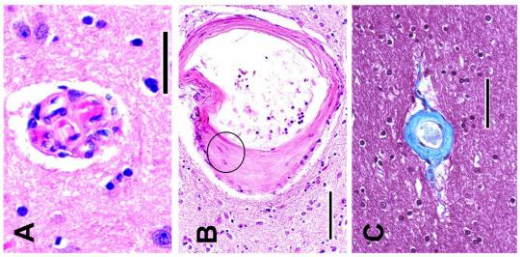


Matthews, et al. PLoS Med 2009;6:e1000180

Cerebral Small Vessel Disease (The Small Stuff)

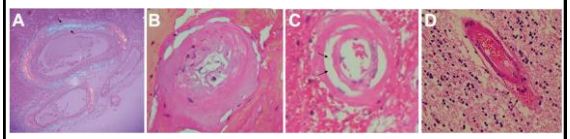
- Pathology: Arteriolosclerosis or Cerebral amyloid angiopathy.
- Consequences: Loss of vascular integrity (bleeding), ischemia (infarction), altered vascular reactivity (disturbed blood flow regulation?).

Arteriolosclerosis



Smith, E. E. and R. N. Auer (2010). Hypertensive Arteriopathy. Microbleeds: From Pathophysiology to Clinical Practice. D. Werring. Cambridge, Cambridge University Press.

Cerebral Amyloid Angiopathy

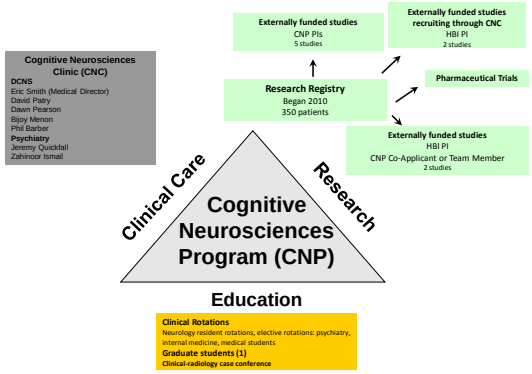


- Accumulation of beta-amyloid in the media and adventitia of small arteries in the cortex and leptomeninges.
- Loss of vascular integrity.
- Cause of lobar intracerebral hemorrhage in older persons
- Associated with cognitive impairment.

Chen Y-W, Lee M-J, Smith EE. Cerebral amyloid angiopathy in East and West. International Journal of Stroke. 2010.

Three Major Questions

1. Can we diagnose the pathologies that cause dementia in living people?
2. Does preventing amyloid build up prevent AD?
3. Does treating vascular risk factors prevent dementia?



Overview of My Research

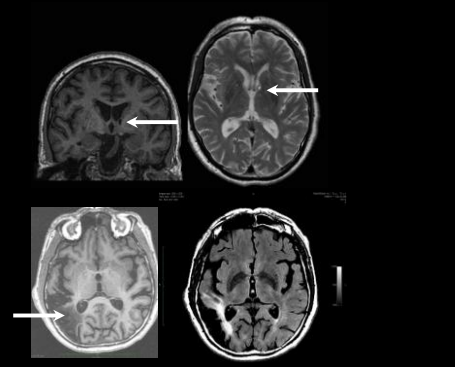
Overall objective: to improve our understanding of cerebral small vessel disease by:

a) Measuring the prevalence and impact of small vessel diseases in the community throughout the lifespan (PURE-MIND study)

b) Improving diagnosis of small vessel diseases in persons with cognitive symptoms at risk for dementia (BRAIN-IMPACT study)

c) Understanding the mechanisms by which small vessel diseases impact brain blood flow, structure and function (FAVR study).

Covert Brain Infarcts

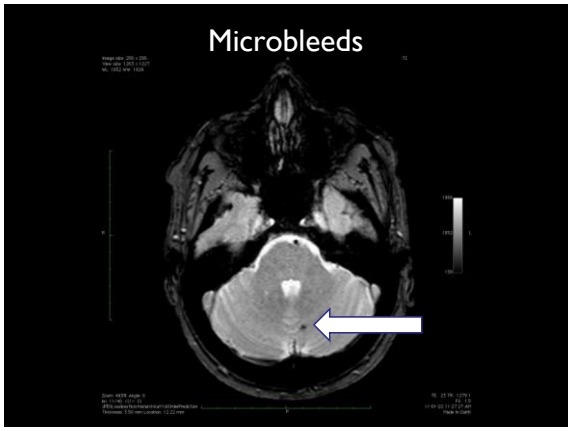


White Matter Lesions

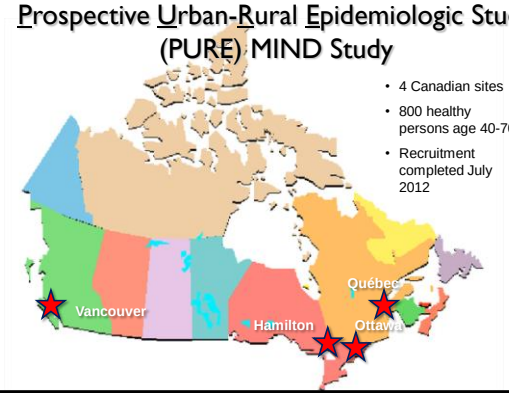
Volume =15.1 mL

- Also sometimes called leukoaraiosis.
- Predominantly represent ischemic demyelination caused by arteriolosclerosis or perivenous collagenosis.

Microbleeds



Prospective Urban-Rural Epidemiologic Study (PURE) MIND Study



- 4 Canadian sites
- 800 healthy persons age 40-70
- Recruitment completed July 2012

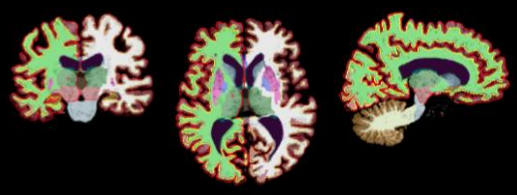
Study Objectives

- What is known: covert infarcts and white matter lesions of presumed vascular origin are seen in elderly preceding dementia.
- Objectives of PURE-MIND:
  - Prevalence of cerebral small vessel disease in 40-70 yrs.
  - Earliest changes in cognition and brain structure caused by vascular risk and covert small vessel disease.

PURE-MIND Study Design

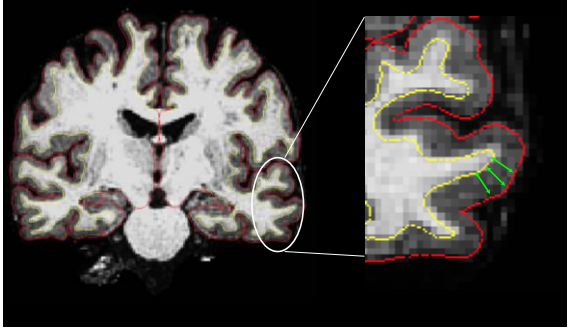
- Longitudinal cohort study.
- Population-based recruitment in communities centred around Vancouver, Hamilton, Ottawa and Quebec.
- Substudy of the Prospective Urban Rural Epidemiological Study (PURE).
- Participants are 40-70 without stroke or dementia.
- Measurements: brain MRI, MoCA, Digit Symbol Substitution test, gait speed and instrumental activities of living (SAGE).
- Pilot phase (n=800) completed funded by CSN, HSFC and CIHR.

BRAIN ATROPHY



Segmented brain produced by FreeSurfer.
Red line indicates pial surface, yellow line white matter/gray matter surface.

CORTICAL THICKNESS

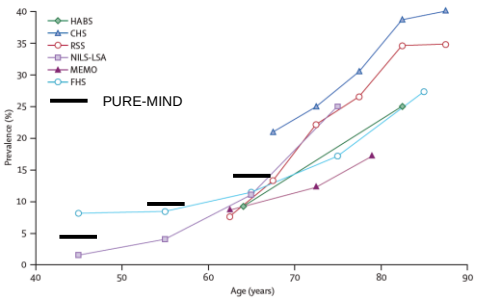


Prevalence of Small Vessel Disease by Age

Age	N	Infarcts (%)	Microbleeds (%)	Extensive white matter lesions[1] (%)	Any of either infarcts, microbleeds or white matter lesions (%)
40-49	250	3.2	2.0	1.3	6.4
50-59	307	9.8	4.9	7.1	18.8
60-70	243	12.8	9.1	23.3	34.9

Smith EE et al. Rationale, design and preliminary findings of the Prospective Urban-Rural Epidemiologic Mind (PURE-MIND) MRI study. 2011: oral presentation at the Canadian Stroke Congress (abstract).

Prevalence of Covert Brain Infarcts by Age



From Vermeer SE, Longstreth WT, Jr., Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol. 2007;6:611-619

Impairments Associated with Covert Infarcts

Characteristic	Covert Infarct (n=69)	No Covert Infarct (n=731)	P value
Age (years)	**59.1 ± 7.6**	**54.1 ± 7.9**	**<0.001**
Male sex	48%	41%	0.31
MoCA total score*	**26 [25, 28]**	**27 [25, 28]**	**0.03**
MoCA ≥26	59%	69%	0.10
Normal MoCA visuospatial/executive subscore†	**42%**	**57%**	**0.02**
Digit Symbol Substitution Test*	**63.0 ± 16.8**	**70.1 ± 15.8**	**<0.001**
CES-D††	4 [1, 10.5]	4 [2, 9]	0.69
CES-D ≥16	12%	10%	0.68
Timed gait (sec)‡	**8.3 ± 4.1**	**7.3 ± 2.0**	**<0.001**
Mild cognitive impairment	14%	9%	0.14

Risk Factors for Covert Infarcts

Characteristic	Covert Infarct (n=69)	No Covert Infarct (n=731)	P value
Age (years)	59.1 ± 7.6	54.1 ± 7.9	<0.001
Male sex	48%	41%	0.31
Diabetes mellitus	10%	6%	0.18
Cigarette smoker			
Current	14%	7%	0.02
Former	45%	39%	
Never	41%	54%	
Systolic BP	138 ± 16 mmHg	128± 16 mmHg	<0.001
Diastolic BP	83 ± 10	79 ± 10	0.002
Waist:hip ratio	0.90±0.09	0.87±0.10	0.02
Body mass index	28.7 ± 5.9	26.8 ± 5.2	0.003

Small Vessel Disease and MCI

- Cerebral small vessel disease is a surprisingly strong contributor to the risk of dementia.
- However, there has been little research on how small vessel disease contributes to conversion from MCI to AD.
- How does AD interact with small vessel disease to cause cognitive decline in MCI?

Brain Imaging and NeuroPsychological Assessment of Cognitive Impairment (Brain-IMPACT)

- Design: Observational prospective cohort study.
- Outcome: Neuropsychological test performance.
- 66 patients in Calgary, 100 in Boston.
- Study procedures: MRI, neuropsychological testing, PIB-PET (Boston cohort only).
- Funding: U.S. NIH, Alberta Heritage Fund for Medical Research.
- Study completion anticipated in March 2013.

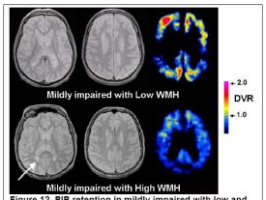
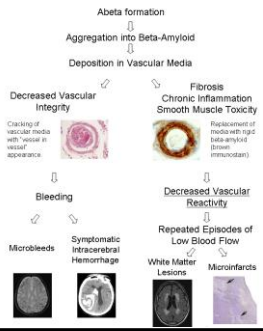


Figure 12. PIB retention in mildly impaired with low and high WMH. PIB retention, similar in degree to that seen in Alzheimer's disease, in mildly impaired subject from MGH Study of Memory and Aging with low WMH volume (top). Conversely only non-specific PIB retention, similar in degree to that seen in PIB-negative normal controls, is seen in mildly impaired subject with high WMH (bottom). We hypothesize that WMH and PIB retention are independently associated with cognition in mildly impaired subjects.

Hypotheses:

- Small vessel disease and AD are competing risks for developing MCI.
- MCI patients with SVD will have greater impairment in processing speed and executive function.
- Small vessel disease and AD will independently predict decline, but the rate of decline will be faster in AD.

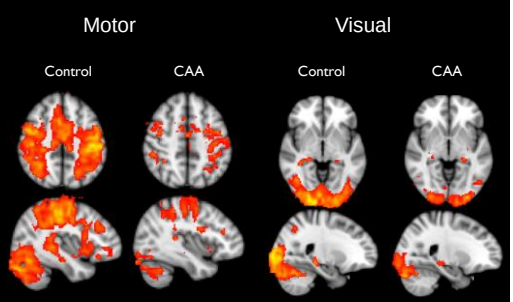
Blood Flow Regulation in Cerebral Amyloid Angiopathy (CAA)



Objectives:

1. To determine whether blood flow regulation is disturbed in cerebral amyloid angiopathy compared to Alzheimer's disease and arteriosclerotic disease.
2. To identify the cognitive profile of CAA compared to AD, mild stroke, and healthy controls.

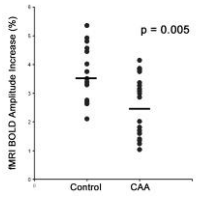
fMRI Activation



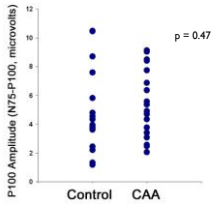
18 CAA (diagnosed by Boston criteria) compared to 18 age and sex-matched controls

Vascular-Neuronal Decoupling in CAA

Visual fMRI BOLD amplitude



Visual Evoked Potential Amplitude



Means

Control: 3.57

CAA: 2.57

Summary

- Cerebral small vessel disease is common and is a surprisingly strong contributor to late-life dementia, although not usually the sole cause of dementia.
- We use neuroimaging to study the prevalence and consequences of cerebral small vessel disease in the general population and in high-risk groups, and in selected patients with cerebral small vessel disease to understand mechanisms of the disease.

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PURE-MIND Study
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