



VASCULAR DEMENTIA AND INDIGENOUS POPULATIONS OF NORTH AMERICA

NAD-RCMAR EVENT

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Why Vascular Dementia Matters

- Dementia is the source of abundant suffering.
- Vascular Cognitive Impairment is a major cause/contributor to Dementia.
- Highly associated with modifiable risk factors

Important questions for Indigenous Populations

- Prevalence?
 - Challenges in measuring?
- Differences in risk factors?
- Differences in prevalence of risk factors?
- Unique challenges in risk reduction?
 - Access to healthcare
 - Awareness in the community

OBJECTIVES

- Vascular cognitive impairment: Prevalence in Indigenous populations in North America.
- Cerebrovascular anatomy and physiology.
- Nomenclature and history.
- Pathobiology of Vascular Cognitive Impairment.
- Clinical characteristics.
- Relationship to Alzheimer Disease.
- What is current state of knowledge with regards to Indigenous populations.

Prevalence in US

- 40% of brains from individuals with dementia have concomitant cerebrovascular disease.
- 10% of brains from individuals with dementia show evidence of Cerebrovascular disease alone.
- 50% of brains with Alzheimer pathology also show evidence of cerebrovascular disease.
- Prevalence differs by race.
 - African Americans are about 2x as likely to have AD or other dementias compared to whites
 - Hispanics are about 1.5 x as likely compared to whites
- Disparities
 - “health conditions such as cardiovascular disease and diabetes, which are associated with an increased risk for Alzheimer’s and other dementias, are believed to account for these differences, as they are more prevalent in African-American and Hispanic people.” (Alzheimer’s Association. 2018 Alzheimer’s Disease Facts and Figures. Alzheimer's Dement 2018;14(3):367-429)

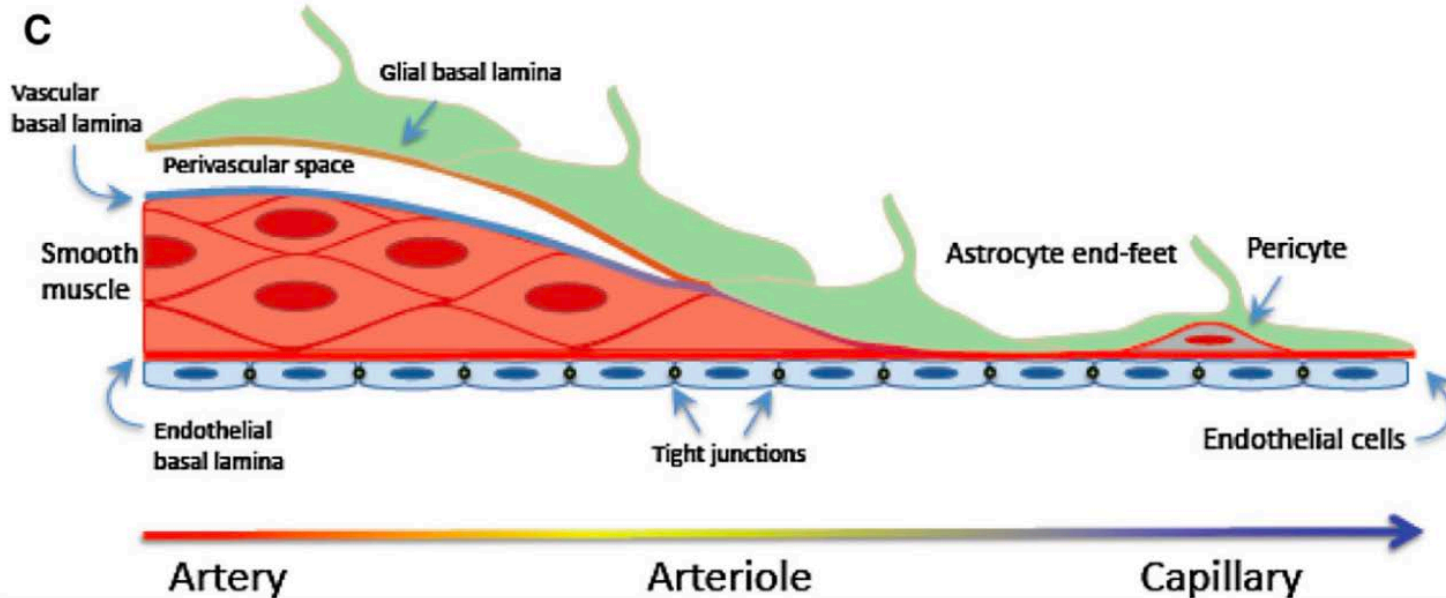
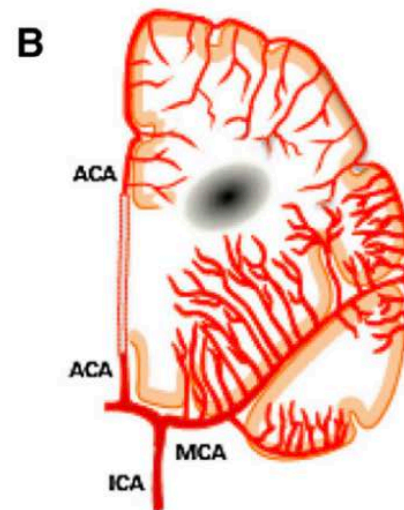
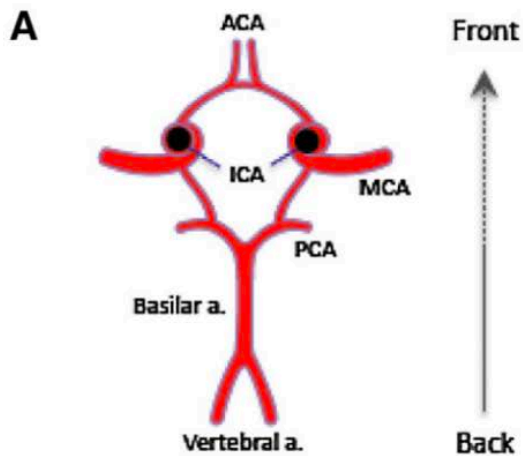
Prevalence in Indigenous populations?

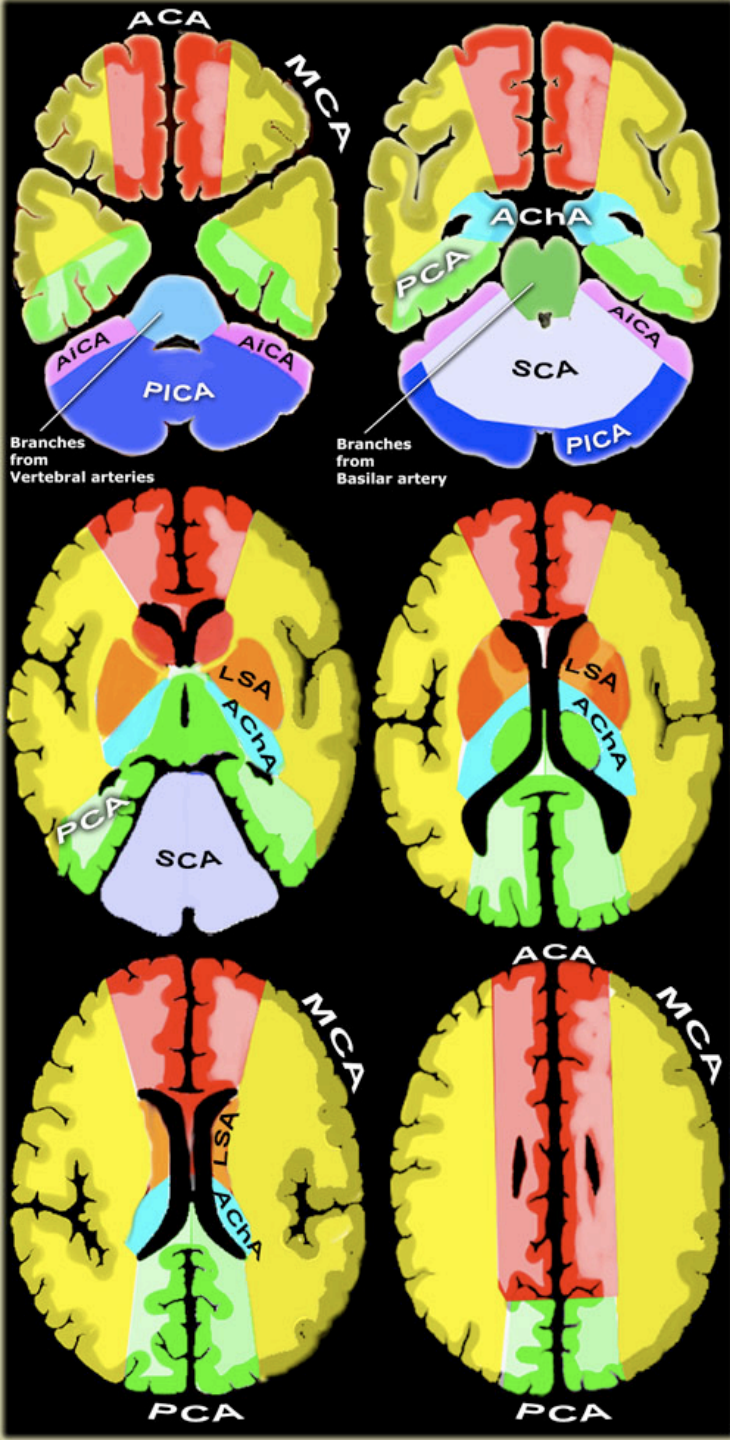
- Prevalence of vascular dementia in indigenous populations of north America is not known.
- All cause dementia incidence is increased in AI/AN and Pacific Islanders.
 - African American (26.6: 1000)
 - AIAN (22.2:1000)
 - Latino (19.6:1000)
 - Pacific Islander (19.6:1000)
 - White (19.3:1000)
 - Asian American (15.2:1000)
- Inferring from other indigenous populations
 - Data from Australia suggests cause of dementia is no different than the general population of Australia.

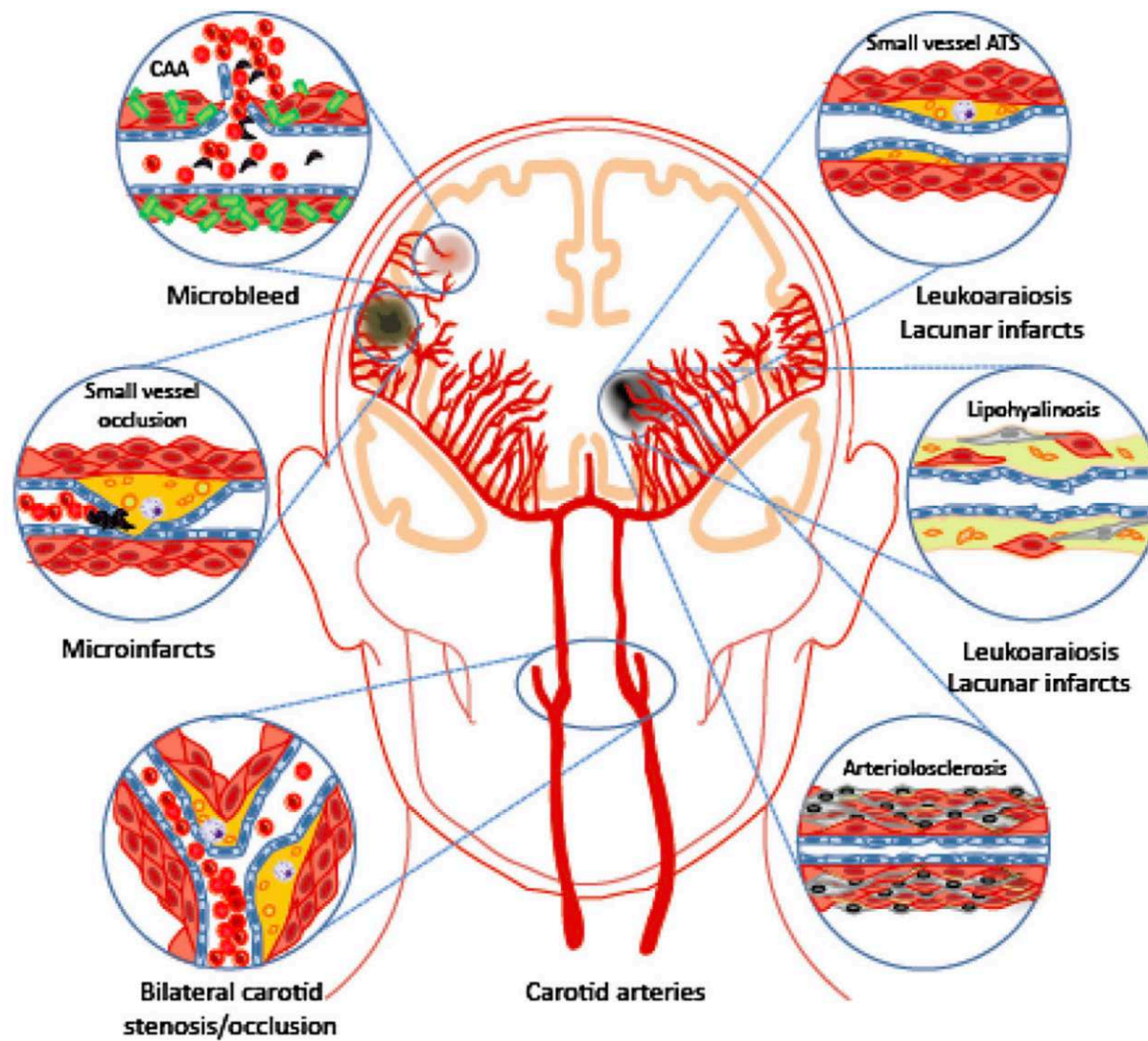
Pathobiology of vascular cognitive impairment

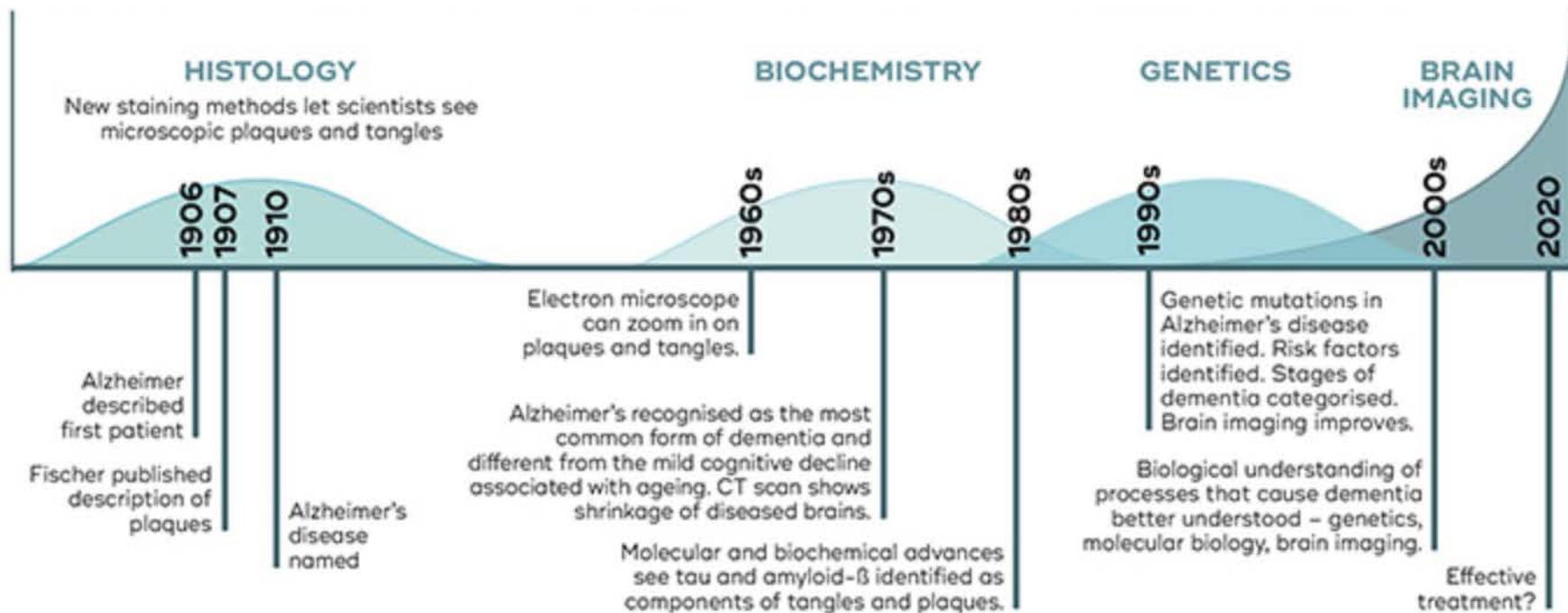
Not just tubes!

- Brain is just 2% of body weight and uses 20% of body energy.
- Energy use is highly dependent neuronal activation.
 - Intricate regulation mechanisms.
- No lymphatics – mechanism of waste removal.
- Blood Brain Barrier
 - Neuroimmunology









Hachinski, V.C., Lassen, N.A., and Marshall, J. (1974).

Multi-infarct dementia. A cause of mental deterioration in the elderly.

Lancet 2, 207–210.

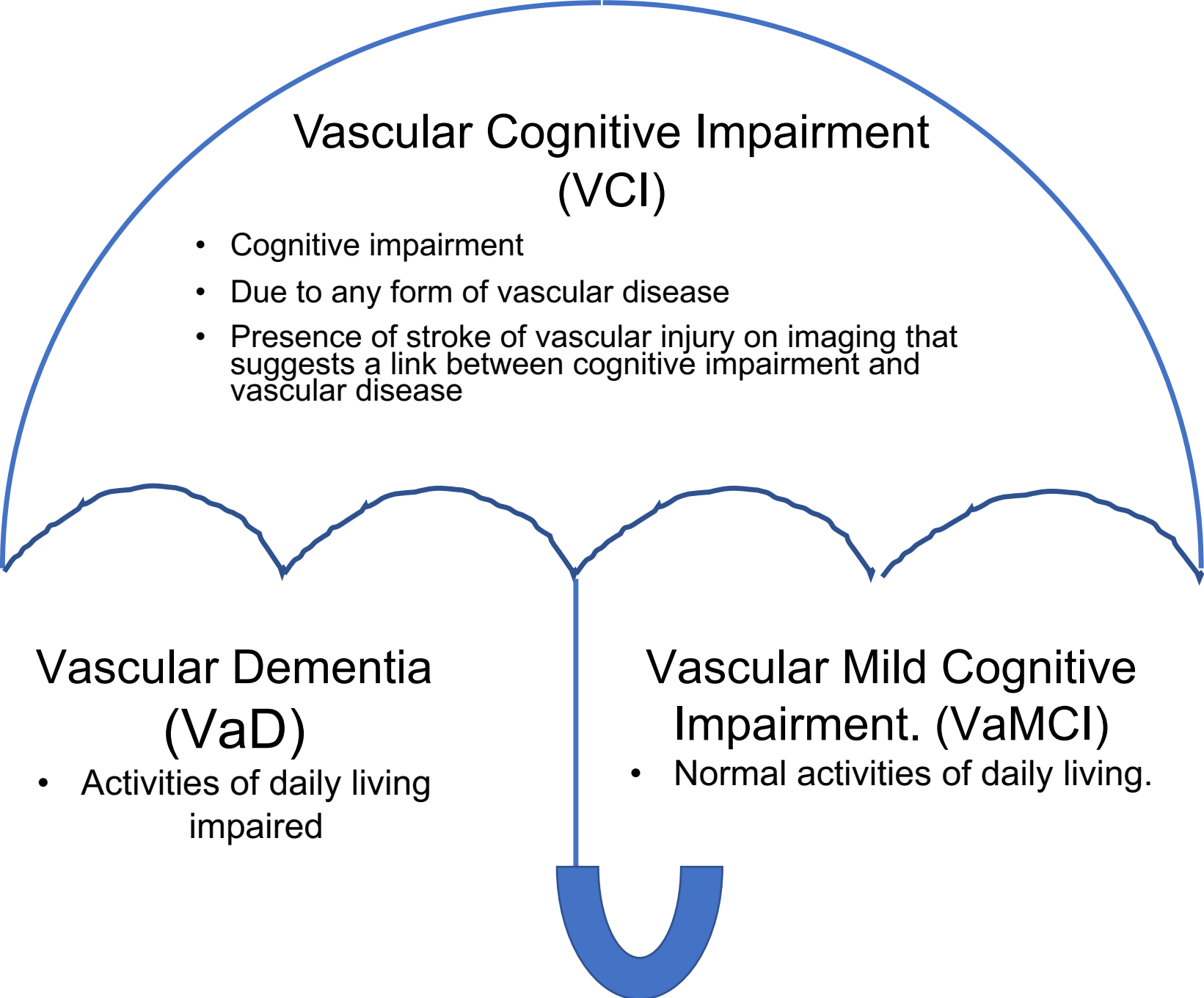


Tomlinson, B.E., Blessed, G., and Roth, M. (1970).

Observations on the brains of demented old people.

J. Neurol. Sci. 11, 205–242.





Vascular Cognitive Impairment (VCI)

- Cognitive impairment
- Due to any form of vascular disease
- Presence of stroke or vascular injury on imaging that suggests a link between cognitive impairment and vascular disease

Vascular Dementia (VaD)

- Activities of daily living impaired

Vascular Mild Cognitive Impairment. (VaMCI)

- Normal activities of daily living.

Vascular Cognitive Impairment (VCI) Subtypes

1 Single or multiple cortical infarcts

- ACA
- PCA
- MCA

2 Ischemic hypoperfusion

- Watershed
 - ACA/MCA
 - MCA/PCA
 - Chronic hypoperfusion

3 Cerebral Small Vessel Disease (CSVD)

- Lacunar State
- Binswanger's disease

4 Strategic subcortical infarcts

- Caudate
- Lenticular
- Capsular Genus
- Thalamus

Single or Multiple Cortical Infarcts

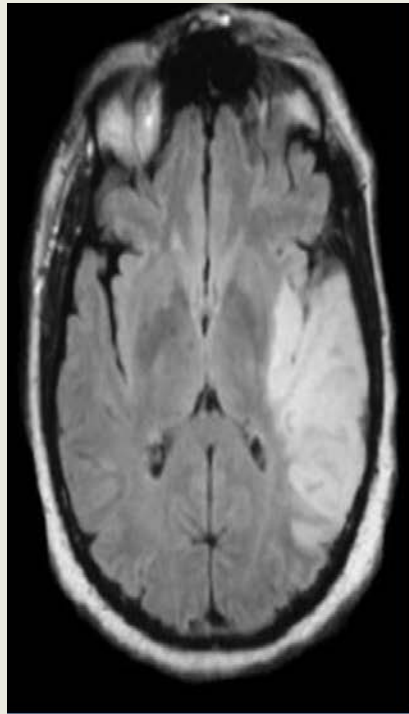
ACA Syndromes

1. Anterior Cingulate
2. Medial Orbitofrontal



MCA Syndromes

1. Dorsolateral Prefrontal
2. Left Hemisphere
3. Right Hemisphere

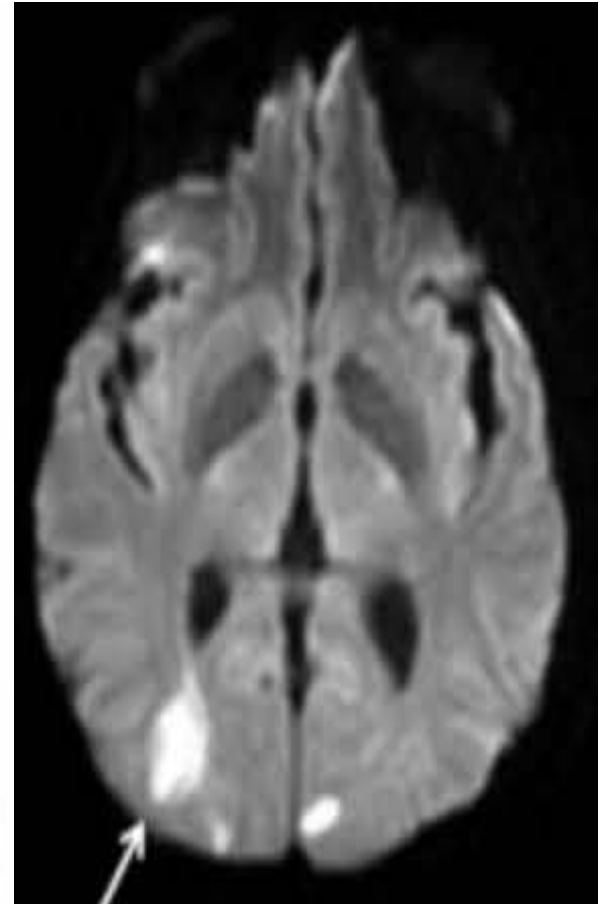
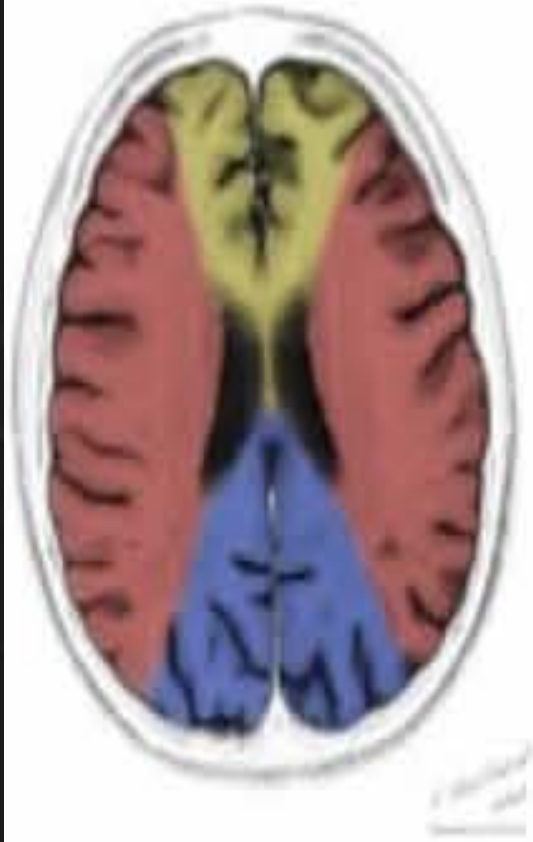
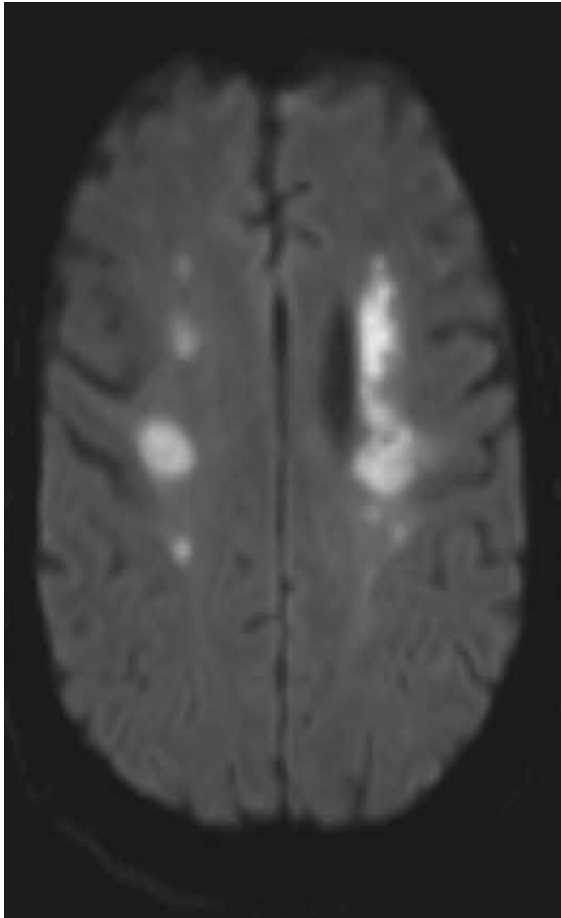


PCA Syndromes

1. Hemianopsia
2. Alexia without agraphia

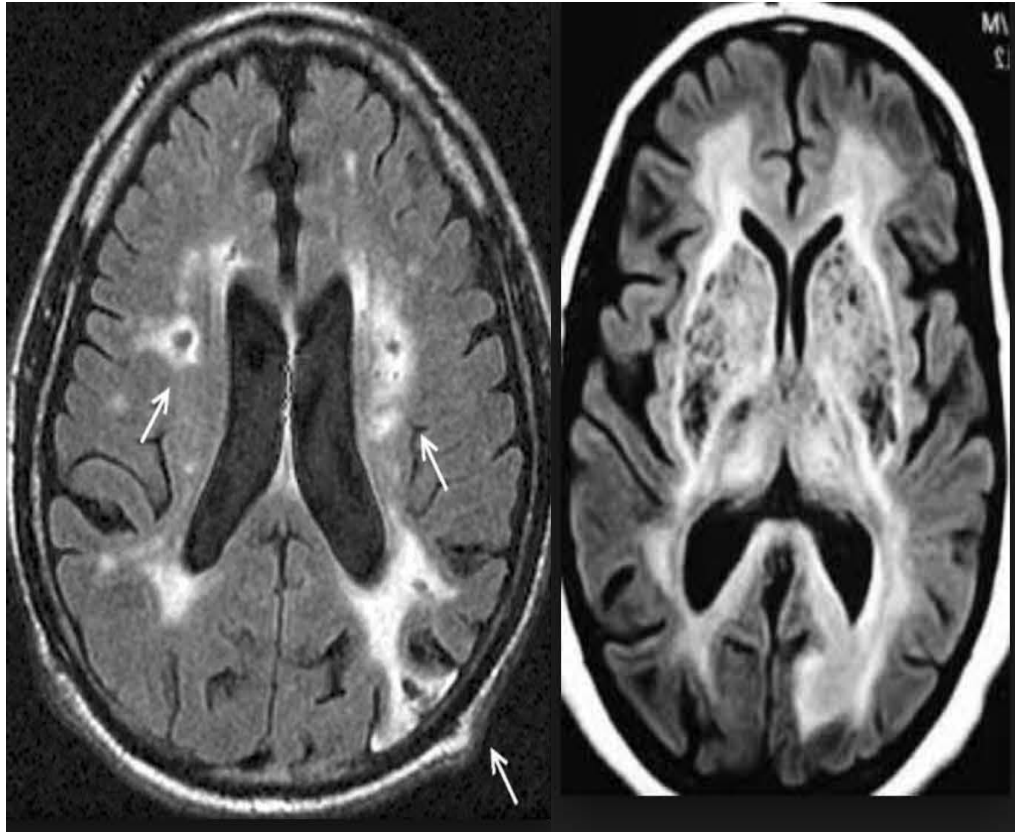


Ischemic Hypoperfusion



Cerebral Small Vessel Disease

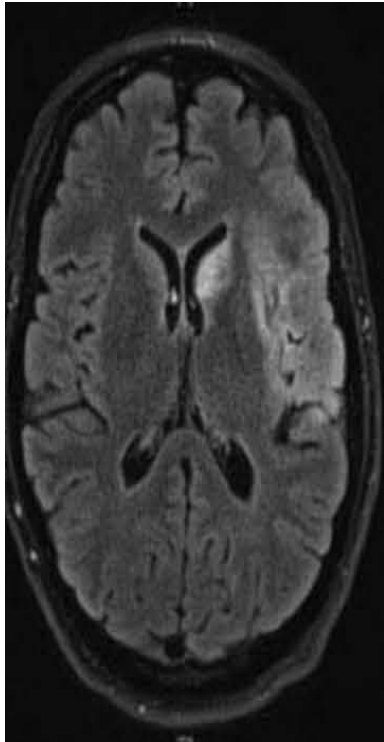
Lacunar
state



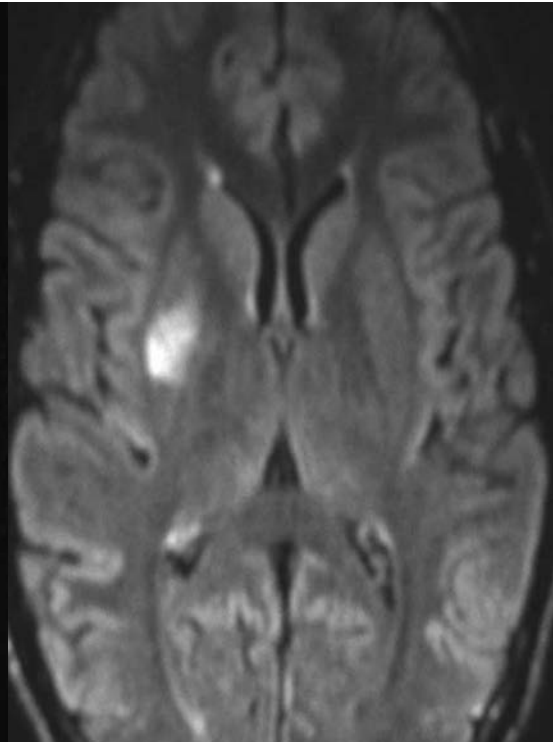
Binswanger's

Strategic Subcortical Infarcts

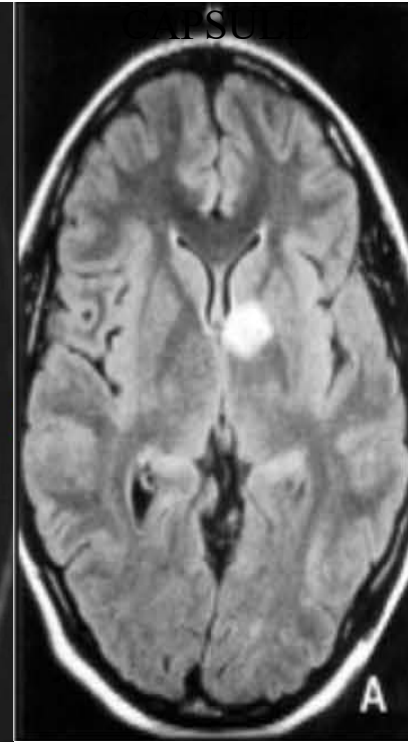
CAUDATE



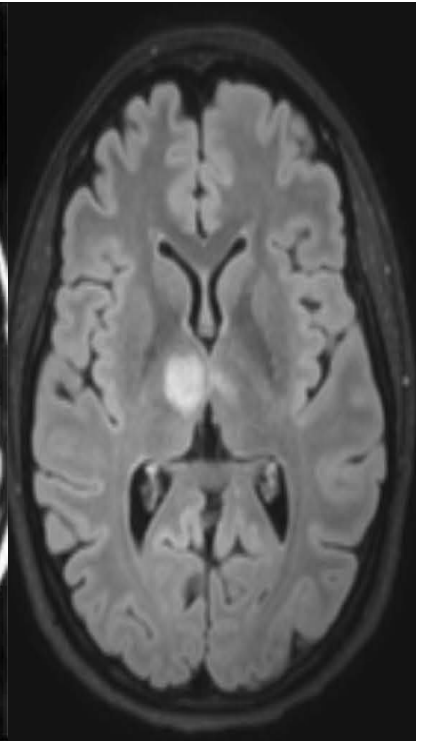
LENTRICULAR



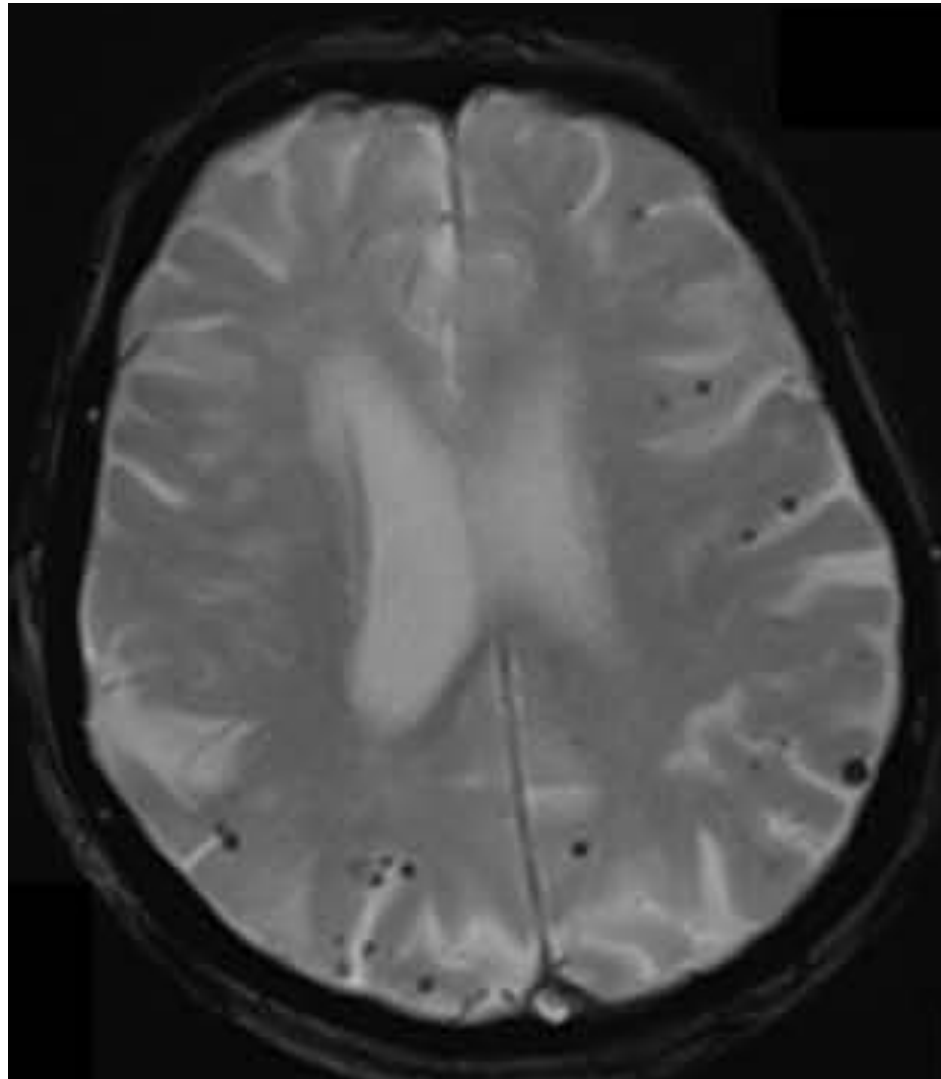
GENU INTERNAL



THALAMIC



Cerebral Amyloid Angiopathy



VCI vs AD

Epidemiology and relationship to Alzheimer's

1. "Mixed Dementia" - 40-50% of dementia cases show evidence of cerebrovascular disease
2. 10% of dementia cases are solely vascular
3. Cerebrovascular disease and Alzheimer's disease share many risk factors

VCI Clinical Characteristics

1. Executive dysfunction
2. Slowed processing speed
3. Memory retrieval deficit
4. Focal motor and sensory deficits
5. Mood – depression, anxiety
6. Stepwise decline

Interactions between cerebrovascular disease and Alzheimer disease pathology

- Alzheimer disease pathology rarely occurs in isolation in clinicopathologic studies (9%)
- Alzheimer pathology is found with at least one other neurodegenerative and vascular pathology (44%) or at least one vascular pathology (40%)
- Alzheimer's, Lewy body and hippocampal sclerosis are the most potent influencers of cognitive function while vascular disease is somewhat less potent.

Summary: Cortical infarcts and cerebrovascular damage in the deep grey matter has the most impact on cognition in the presence of AD pathology.

- Methods: 1355 autopsies from 1993-2003 in Geneva.
- Excluded tumor, PD, macro infarct, Lewy body, synuclein, ubiquitin, AGD
- Final sample n= 156 (age 73-104)
- Results:
 - White matter lacunes, periventricular lesions and diffuse WM demyelination, diffuse and focal cortical gliosis did not seem to impact cognition
 - Braak NFT, ABeta deposition, cortical micro-infarcts and thalamus/basal ganglia lacunes predicted 29% of variability in CDR and 49% of the presence of dementia.
 - Presence of cortical micro infarcts mattered even with severe NFT pathology

Summary: AD is bad for cognition. AD+ cerebrovascular damage in white matter and deep gray matter is worse. Presence of cerebrovascular damage lowers threshold for AD pathology to cause dementia.

- Methods: Sisters of Notre Dame. All white, all women. Enrolled 1991-1993. All had annual battery of cog tests, ADL and social function assessments.
- By 1995 161 dead and neuropath on 146 (15 were too distant to get brains)
- Infarct definition: gross visual on 1.5 cm coronal slices. Lacune 1.5 cm or less, infarct 1.5 cm or greater.
- Results: 61/146 met neuropath criteria for AD
 - Lacunes in basal ganglia, thalamus and deep white matter had especially high prevalence of dementia. OR 20.7 (1.5-288)
 - If you had lacunes in these areas you required less AD path to be demented
 - In 41 who did not meet AD criteria Infarcts were only weakly associated with poor cog function or dementia
 - Of the 41 without AD only 3 had dementia. 1 had proximal MCA infarct and 2 had no clear pathology.

Genetics

- Vascular Dementia, along with Alzheimer dementia is considered to be heavily influenced by environmental and lifestyle factors.
- How heritable is it?

Genetics

- Monogenic diseases (rare, generally young onset)
 - CADASIL
 - CARASIL
 - Fabry Disease
 - stroke, renal disease, cardiomyopathy, neuropathy
 - COL4A1-A2 arteriopathy
 - Retinopathy and cerebral small vessel disease
- } Strokes, rapidly progressive cognitive impairment, seizures and mood disorders.

Genetics

- Sporadic Vascular Cognitive Impairment
 - APOE ϵ 4
 - PON1
 - TNF- α
 - TGF- β 1
 - MTHFR
- Genome Wide Association Studies (GWAS)
 - Multiple variants associated with stroke and white matter hyperintensities but no consistently identified variants associated with Vascular Dementia.

MODIFIABLE RISK FACTORS

Smoking

Hypertension

Hyperlipidemia

Diabetes

Metabolic syndrome

Atrial Fibrillation

What explains disparities in dementia incidence in Indigenous populations?

- Hypothesis 1.
 - unequal rates of risk factors for vascular dementia.
- Hypothesis 2.
 - unequal access to treatments leading to reductions in risk factors for vascular dementia
- Hypothesis 3.
 - Lack of awareness about the association between vascular health and cognitive function or the relationship of vascular health to Alzheimer's disease.

Mortality disparity rates for American Indians and Alaska Natives (AI/AN) in the IHS Service Area 2005-2007 and U.S. All Races 2006 (age-adjusted mortality rates per 100,000 population)

	AI/AN rate 2005-2007	U.S. All-race rate 2006	Ratio: AI/AN to U.S. all races
All causes	953.7	776.5	1.2
Alcohol induced	45	6.9	6.5
Breast cancer	19.6	23.5	0.8
Cerebrovascular	43.8	43.6	1
Cervical cancer	2.8	2.4	1.2
Diabetes	65.6	23.3	2.8
Heart disease	191.7	200.2	1
HIV infection	3.2	4	0.8
Homicide (assault)	11	6	1.8
Infant Deaths †	7.3	6.7	1.1
Malignant neoplasm	170.1	180.7	0.9
Maternal deaths	20.2	13.3	1.5
Pneumonia/influenza	24.3	17.8	1.4
Suicide	19	10.9	1.7
Unintentional injuries*	94.8	39.8	2.4

“The prevalence of diabetes is higher among the American Indian and Alaska Native population (16.5 per cent) than any other major racial or ethnic group in the United States, and the prevalence of diabetes has been increasing.”

Lessons from other disparately impacted populations

Yaffe, K. Et al. **Effect of socioeconomic disparities on incidence of dementia among biracial older adults: prospective study.** BMJ 2013;347-356.

Summary: “SEC is the biggest factor in explaining difference in “Dementia” but some other factors are also relevant.”

- 2457 older adults (70-79 at enrollment), (mean age 73.6, 41.9% black, 50.2% women). Not demented at baseline.
- Beginning in 1997.
- Cohort from “The health, Aging and Body composition study.” Followed for 12 yrs.
- Outcome: Dementia
- Results: Dementia incidence for blacks was 20.7 percent and for whites 16.7%
- Demographics, APOE4 status, comorbidities and lifestyle accounted for some of the difference but African Americans still 40% higher risk. Factoring in SES accounted for 80% of the difference and difference in incidence was no longer statistically significant.

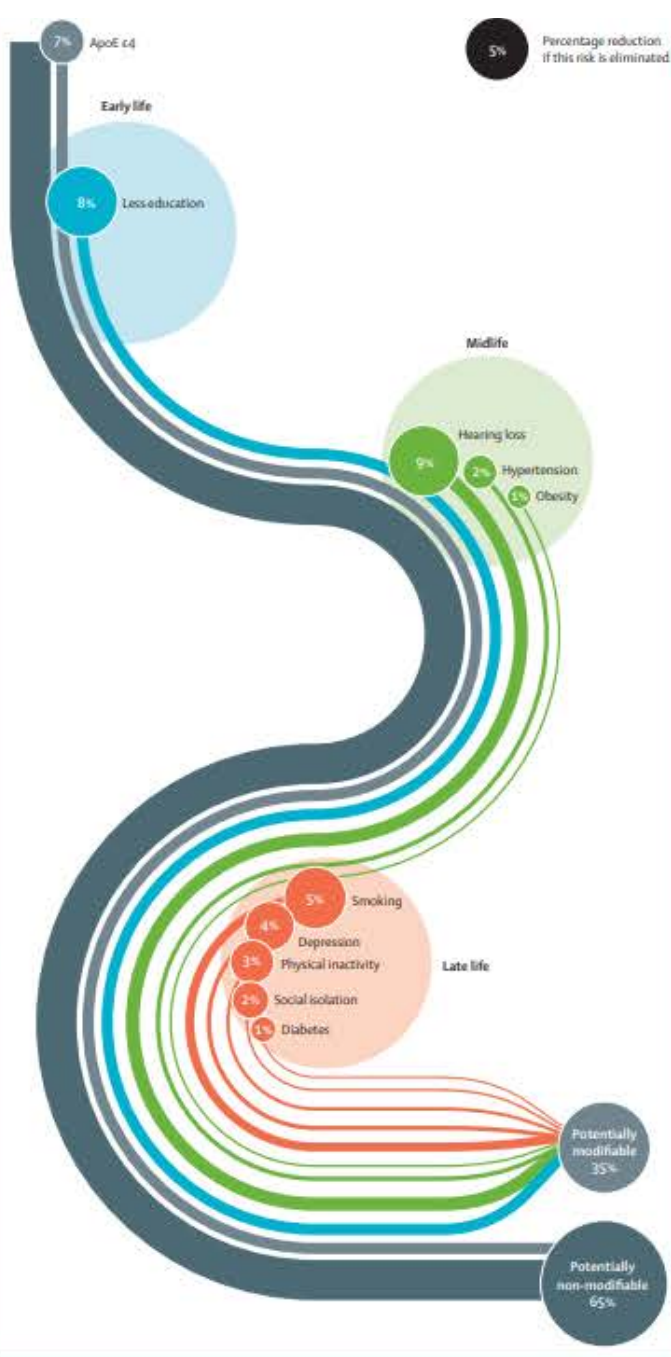
So...

- Prevalence of Dementia is likely higher for indigenous populations.
- Prevalence of at least some risk factors for vascular dementia are likely higher for indigenous populations.
- Prevalence of vascular dementia, as a proportion of all cause dementia is probably not all that different in minority communities if life expectancy is similar.
- Specific knowledge relevant to vascular dementia in indigenous populations of North America is not available.

Prevention?

Modify - what is modifiable!

- Nutrition
 - Diet
 - Supplements
- Risk Factor Reduction
 - Blood pressure
 - Atrial fibrillation
 - Smoking
 - Diabetes
 - Stroke
 - Hyperlipidemia
- Educational Attainment/Intellectual activity



“Interventions for other risk factors including more childhood education, exercise, maintaining social engagement, reducing smoking, and management of hearing loss, depression, diabetes, and obesity might **have the potential to delay or prevent a third of dementia cases.**”

Figure 4: Life-course model of contribution of modifiable risk factors to dementia
Numbers are rounded to nearest integer. Figure shows potentially modifiable or non-modifiable risk factors.

THE FINGER STUDY:

- **A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people**
- Dietary counseling, physical exercise program, cognitive training, management of metabolic and vascular risk factors.
- Diet: >400 grams fruits and vegetables, whole grains, low fat milk and meat products, less than 50 mg sucrose, vegetable margarine or rapeseed oil instead of butter, 2 portions of fish per week (3 individual counseling session and 6 group sessions)
- Results: improvement in executive function but not global cognition.
- **Improvements in executive function and processing speed but no impact on memory.**

Nutrition

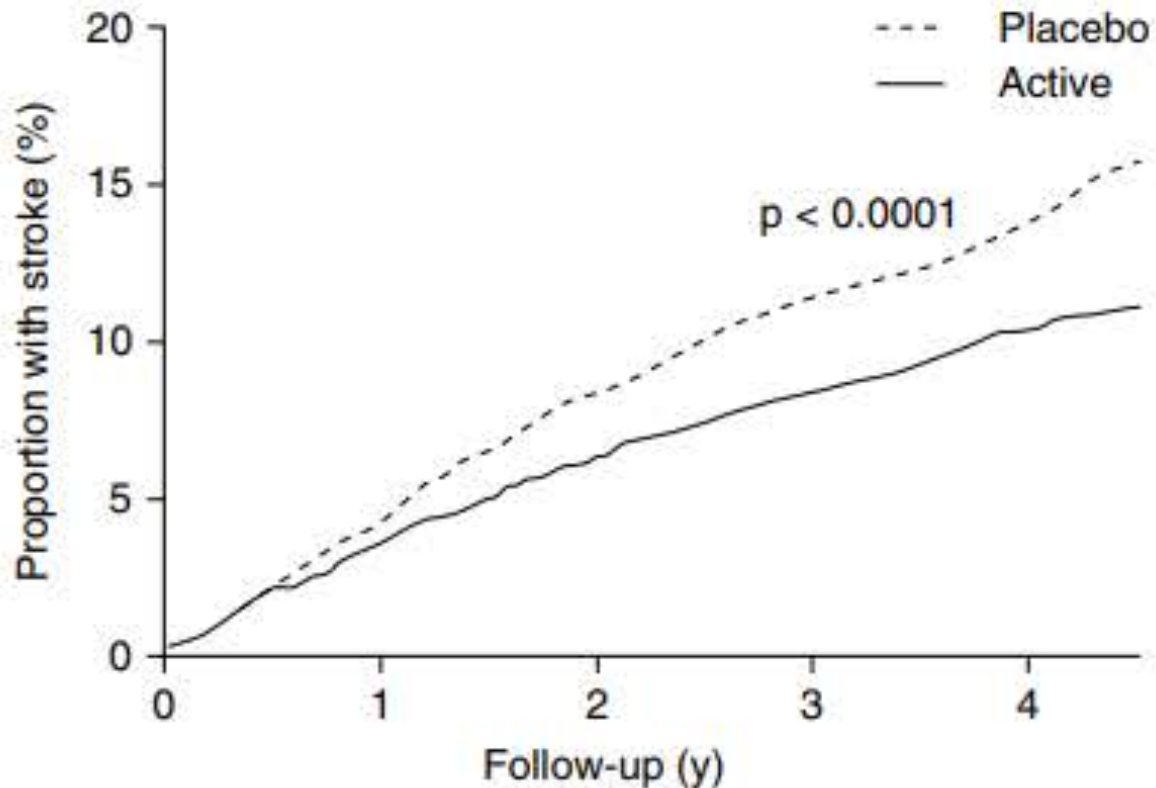
- **PREDIMED**

- 5 years randomized controlled trial.
- Older adults
- Mediterranean diet supplemented with extravirgin olive oil or mixed nuts vs control diet (advised to reduce fat)
- Cognitive testing at baseline and at 4 years.
- Results: cognition improved in the intervention diet and declined in the control diet. Improvements were independent of sex, age, energy intake, education, APOE genotype and vascular risk factors.

Hypertension

- PROGRESS (can BP control reduce Stroke?)
 - Randomized Placebo Controlled trial.
 - Older individuals with history of cerebrovascular disease. BP lowering with ACE inhibitor vs Placebo.
 - Results: 29% reduction in stroke.
- Syst-Eur (Can BP control Reduce Dementia?)
- Randomized Placebo controlled trial
- Antihypertensive Treatment vs no treatment
- Stopped early because of significant benefit in stroke reduction.
- Open label extension allowing control group to start antihypertensive
- Results: risk of dementia reduced by 55% by treating hypertension. Treatment of 1000 individuals for 5 years can prevent 20 cases of dementia (95% CI 7-33).

- PROGRESS (can BP control reduce Stroke?)
 - Randomized Placebo Controlled trial.
 - Older individuals with history of cerebrovascular disease. BP lowering with ACE inhibitor vs Placebo.
 - Results: 29% reduction in stroke.



- Syst-Eur Study

Randomized Placebo controlled trial
Antihypertensive Treatment vs no
treatment

Can BP control
Reduce
Dementia?

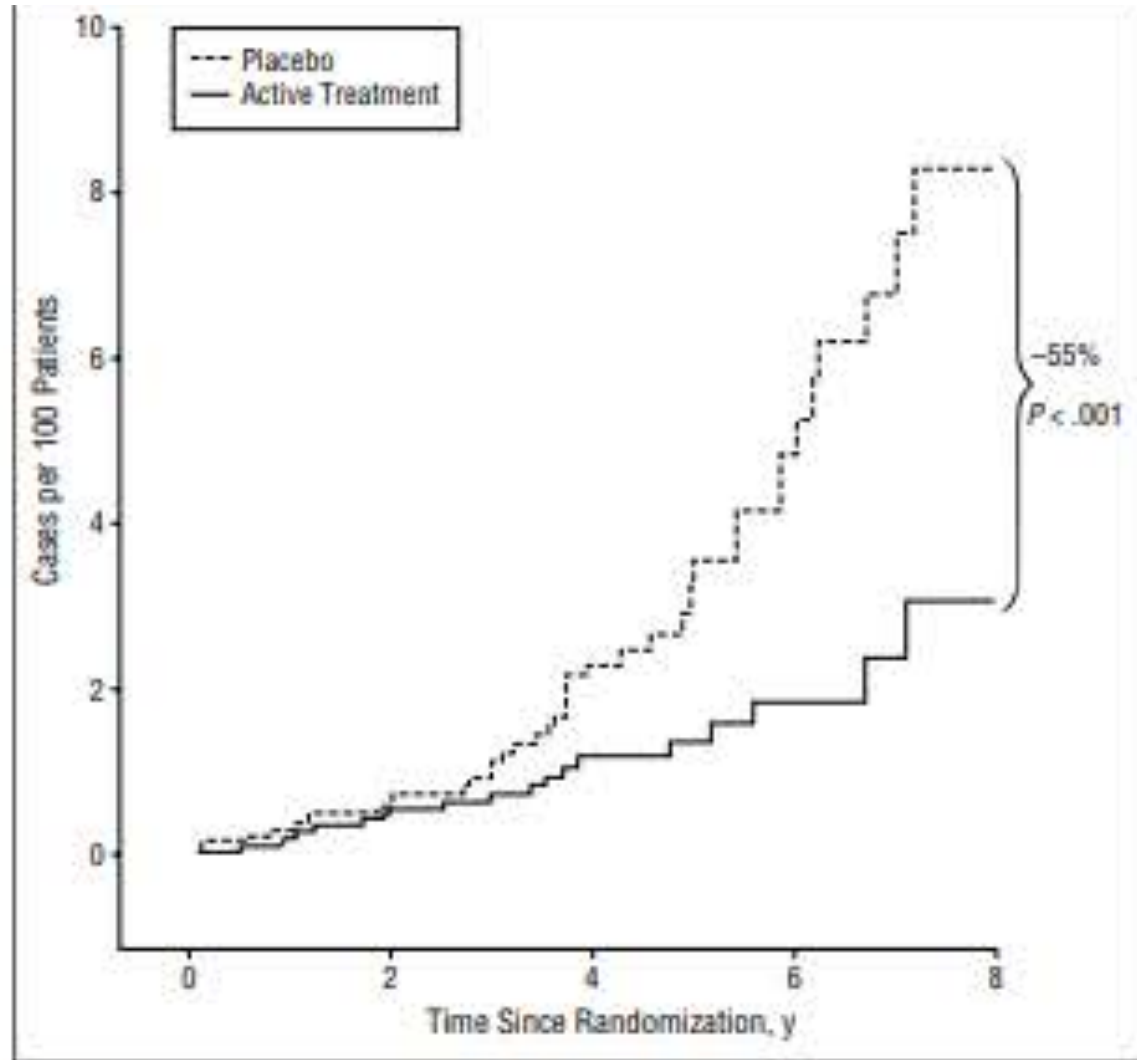


Figure 3. Culmulative rate of dementia by treatment group.

Summary

- VCI is common.
- VCI is one of the most preventable causes of cognitive impairment.
- Cerebrovascular disease interacts with other neuropathologies (especially AD) to determine severity of dementia.
- Estimates of VCI for North American Indigenous populations are not available.
- Risk factors for VCI are higher for indigenous populations but this alone does may not explain the difference in dementia prevalence.

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