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DIABETES AND VASCULAR DEMENTIA

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- Dr. King joined the University of Utah in September 2009 as Assistant Professor in the Department of Neurology in the Center for Alzheimer's Care, Imaging and Research (CACIR), where he also serves as Director of the Alzheimer's Image Analysis Laboratory. Dr. King received a Bachelor's in Bioengineering from Texas A&M University, where he graduated cum laude, and with University and Foundation honors. He received his PhD in Neuroscience and his MD from the Baylor College of Medicine in Houston, Texas, where he also interned in internal medicine. In 2002, he was honored with the First Annual Richard R. Dickason Outstanding Physician Scientist award from Baylor College of Medicine's Medical Scientist Training Program. He completed his neurology residency at Harvard Medical School in Massachusetts, followed by a fellowship in Behavioral Neurology and Cognitive Neuroscience at the University of Texas at Dallas. In October 2008, Dr. King completed a six-week mini-fellowship in Cognitive Disorders at the University of Utah.

Dementia (from DSM-IV)

- ⊙ The development of multiple cognitive deficits manifested by both:
 - Memory impairment
 - One or more following disturbances
 - Aphasia
 - Apraxia
 - Disturbance in executive function
 - Agnosia
- ⊙ Cognitive deficits each cause significant impairment in social or occupational functioning
- ⊙ Subtypes (in DSM-IV)
 - Alzheimer's
 - Vascular
 - Due to other medical conditions
 - Substance-inducing persisting dementia
 - Dementia due to multiple etiologies
 - Dementia NOS

Activities of Daily Living

- ◎ Boundary between ‘mild cognitive impairment’ and ‘dementia’
- ◎ ADLs: bathing, toileting, transfer, dressing, eating
- ◎ IADLs (executive functioning):
 - Maintaining household
 - Shopping
 - Transportation
 - Finances

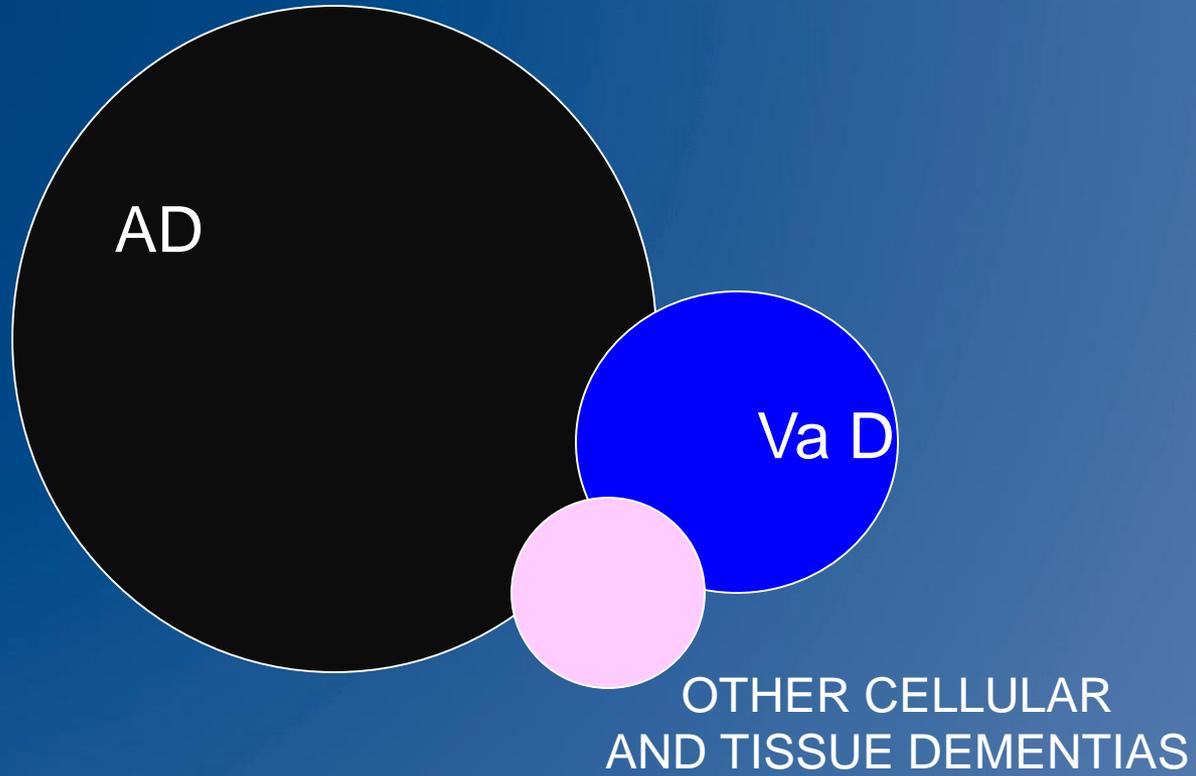
Differential Diagnosis of Dementia

- ⊙ Delirium: acute, clouding of sensorium, fluctuations in level of consciousness, difficulty with attention and concentration
- ⊙ Depression: patient complains of memory loss
- ⊙ Delirium and depression: markers of dementia?

- ⊙ 5% people over age 65 and 35-50 % over 85 have dementia, therefore pretest probability of dementia in older person with memory loss at least 60%

Causes of Dementia

- ⊙ Alzheimer's dementia (AD): 60%
- ⊙ Vascular dementia (VaD): 15-20%
- ⊙ Lewy Body dementia 10%
 - Parkinson's disease dementia
- ⊙ Others (10%)
 - Frontotemporal dementia
 - Behavior or Language variants
 - Corticobasal degeneration
 - Progressive Supranuclear Palsy
 - Prion diseases (CJD)
 - Nutritional deficiencies
- ⊙ Japan/China – VaD is the most common



AD

Va D

OTHER CELLULAR
AND TISSUE DEMENTIAS

History.... (just for fun!)

- 17th century – Thomas Willis described post-apoplectic dementia
- 1894 – Otto Binswanger and Alois Alzheimer differentiated between VaD and neurosyphilis (and sub-categorized VaD into 4 subtypes)
- 1910 – Kraepelin concluded that “arteriosclerotic insanity” was the most frequent form of senile dementia
- 1970s – AD identified as the most common cause of dementia
- At the same time Tomlinson, Blessed and Roth showed that loss of more than 50-100mL of brain tissue from strokes caused cognitive impairment and the term “multi-infarct dementia” was coined

In summary:

- ⦿ Both diffuse and discrete ischemic brain pathological change and their impact on cognitive function were recognized by the turn of the last century.
- ⦿ In the first seven decades of the 20th century, ischemia both chronic and acute was thought responsible for the vast majority of dementia cases.
- ⦿ A cellular basis for dementia was increasingly recognized in the later half of the 20th century, while vascular dementia was recognized primarily in the restricted form of multi-infarct dementia.
- ⦿ Today, vascular dementia is recognized as a heterogeneous group of disorders, each with its own pathophysiologic characteristics. Any of these processes can contribute to a dementing illness, and any could in theory overlap with a cellular dementia.

Semantics...

Vascular Dementia

- Cognitive deficits meet clinical criteria for dementia
- Also has been called: multi-infarct dementia, ischemic vascular dementia, arteriosclerotic dementia, cerebrovascular dementia, ischemic-vascular dementia
- 4 sets of diagnostic criteria: all give you slightly different results

Vascular Dementia

- ◎ Generally clinicians look for
 - Stepwise progression, prolonged plateaus or fluctuating course
 - Focal cognitive deficits but not necessarily memory impairment
 - Impaired executive function (difficulty problem solving, difficulty with judgement)
- ◎ Diagnosis strengthened by
 - Focal neurological signs (weakness on one side, difficulty with speech)
 - Neuroimaging (CT or MRI) consistent with ischemia
 - CV risk factors, concurrent peripheral vascular disease, coronary artery disease etc

Vascular dementia

- ⦿ Onset of cognitive deficits associated with a stroke (but often no clear hx of CVA, more multiple small, undiagnosed CVAs)
- ⦿ Abrupt onset of sx's with stepwise deterioration
- ⦿ Findings on neurological examination
- ⦿ Infarcts on cerebral imaging (but ct/mri findings often have no clear relationship...)

Overlap

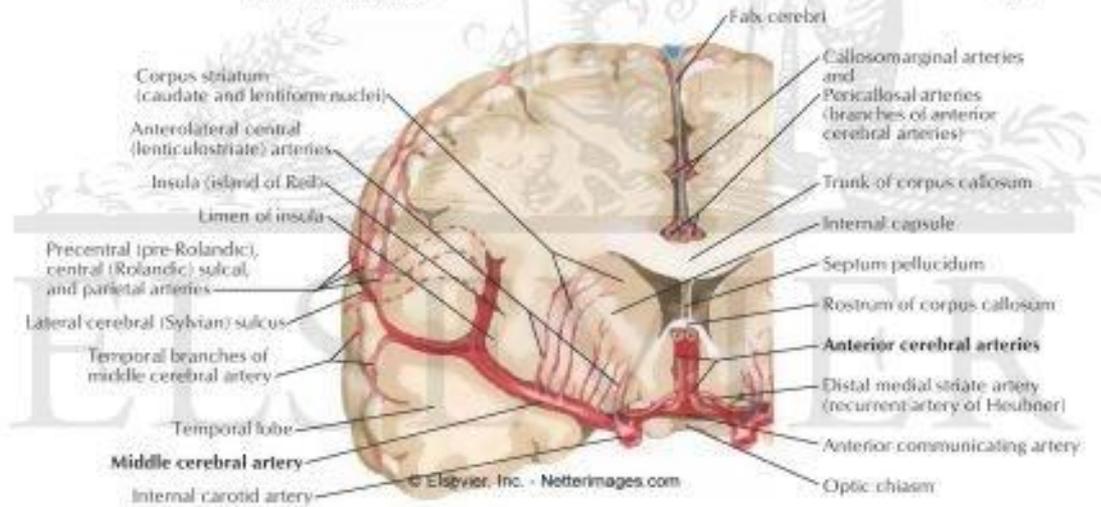
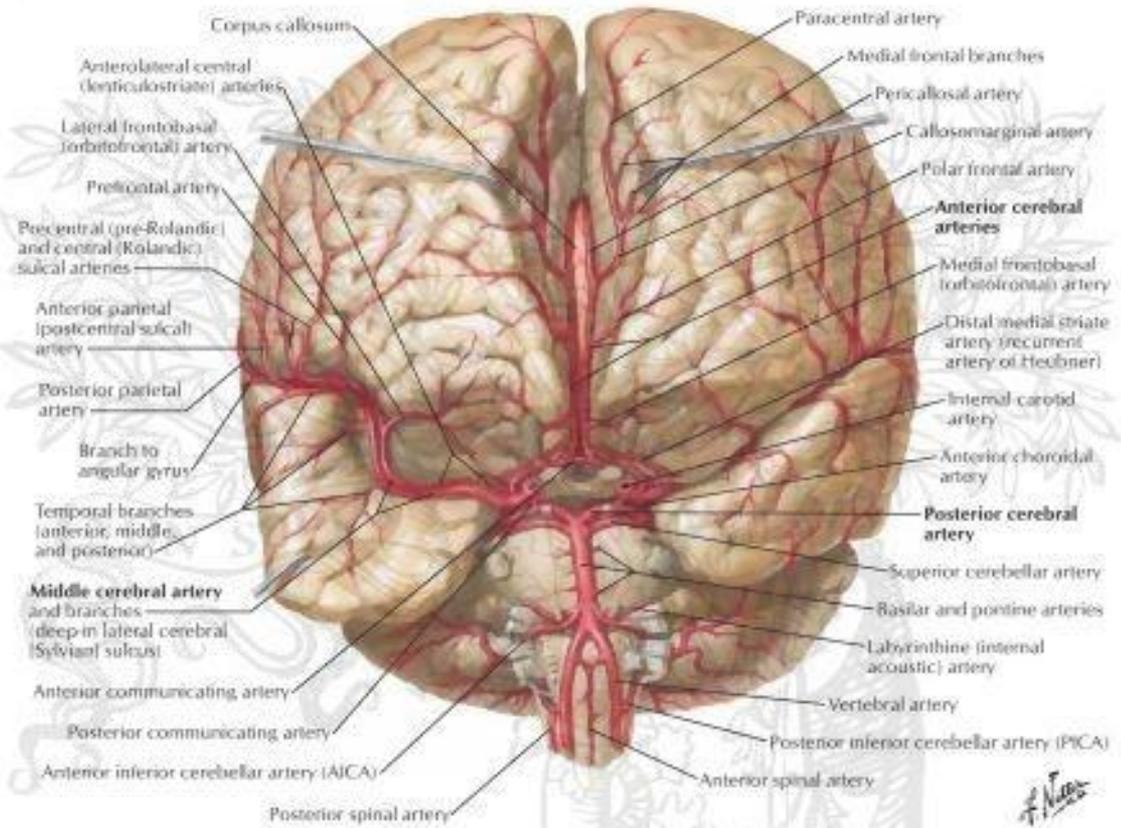
- ⊙ Most patients previously categorized as either Alzheimer type or vascular type dementias probably have BOTH
- ⊙ Likelihood of AD and vascular disease significantly increases with age, therefore likelihood of both does as well...
- ⊙ Vascular risk factors predispose to AD -- ?does it allow the symptoms of AD to be unmasked earlier??

NINDS – AIREN criteria for the diagnosis of vascular dementia

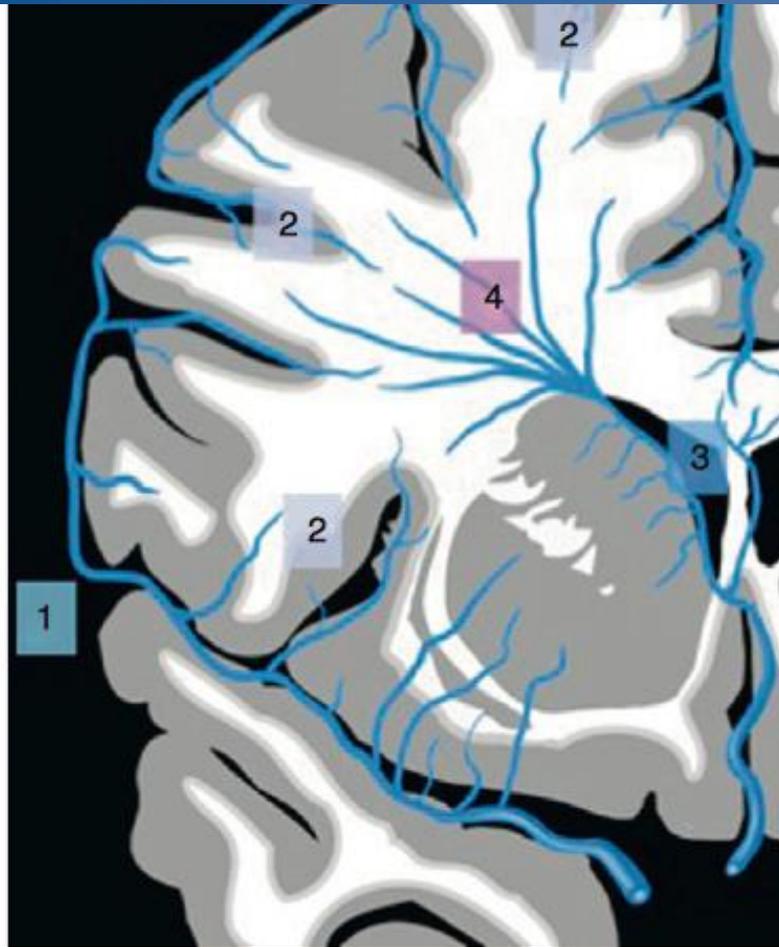
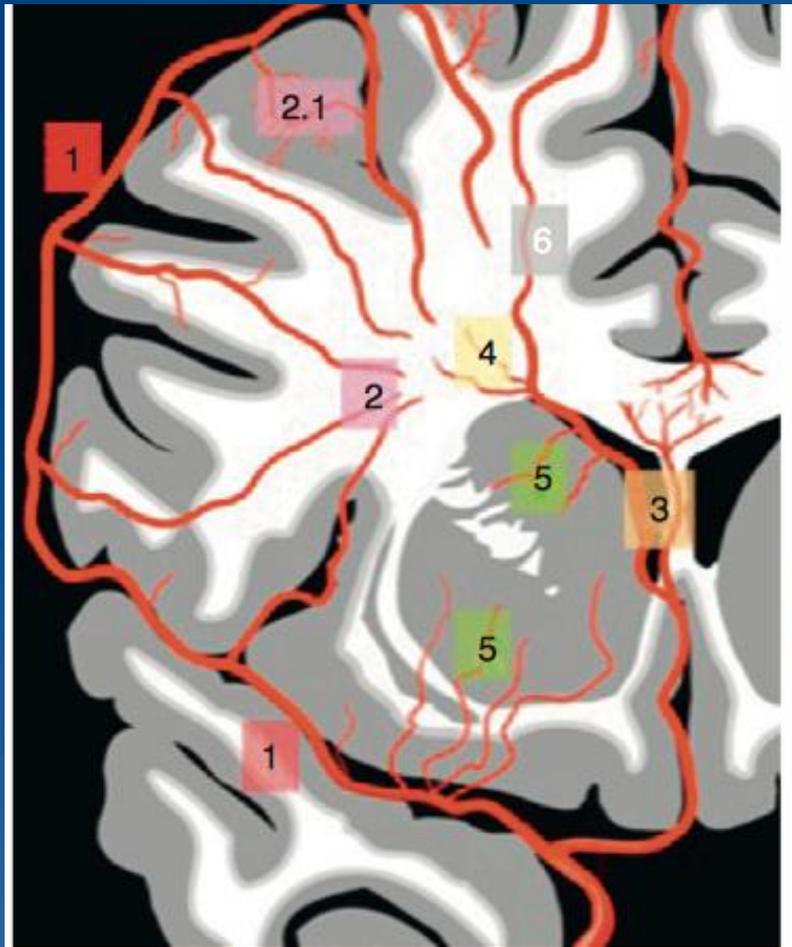
- ⊙ *Dementia* defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains
 - preferable established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.
- ⊙ *Cerebrovascular disease*, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of relevant CVD by brain imaging (CT or MRI)
- ⊙ *A relationship between the above two disorders*, manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

Clinical Categories

- ⦿ Large Vessel Vascular Dementia
- ⦿ Small Vessel Vascular Dementia
- ⦿ Ischemic-Hypoxic Vascular Dementia
- ⦿ Hemorrhagic dementia



Vascular distributions

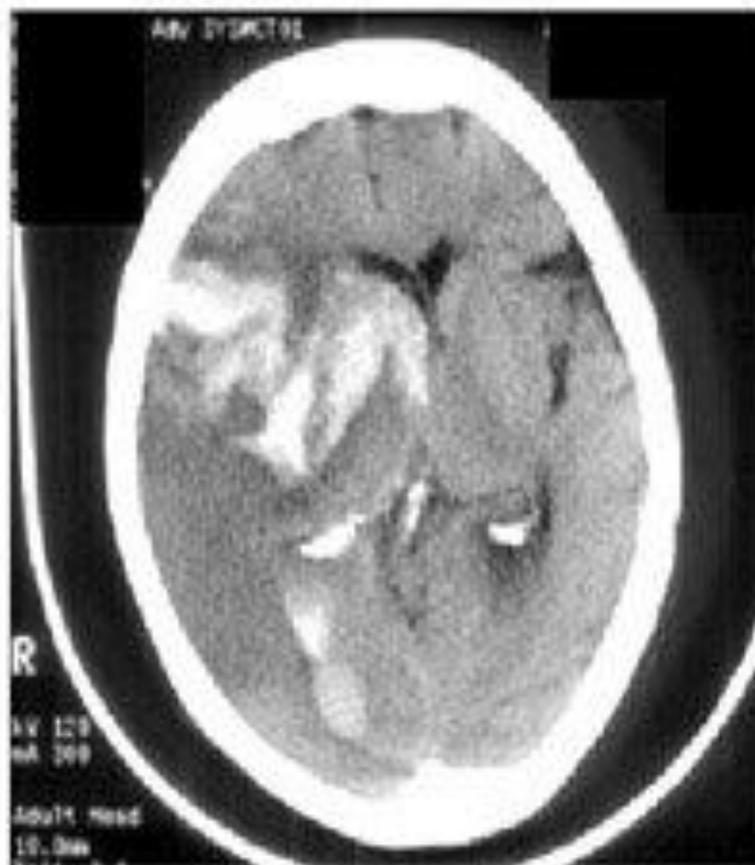


Large Vessel VaD

- ⊙ Post-stroke dementia/ Multi-infarct dementia
 - Dementia developing after multiple completed infarcts
 - Significant proportion of post-stroke dementia remains undiagnosed
- ⊙ Strategic stroke
 - Dementia developing after occlusion of a single large - sized vessel in a functionally critical area
- ⊙ Easiest to recognize, temporal relationship of event and cognitive loss usually evident



Six hours
subtle R MCA infarct



24 hours - the infarct has
undergone extensive
haemorrhagic transformation
after thrombolysis

Large Vessel VaD

- ⦿ Incidence estimates (3 months post CVA) vary: 25-41%
- ⦿ Clinical features will depend largely on what part of the brain was damaged
- ⦿ Depression common
- ⦿ Location of vascular lesion is likely more important than how much tissue died

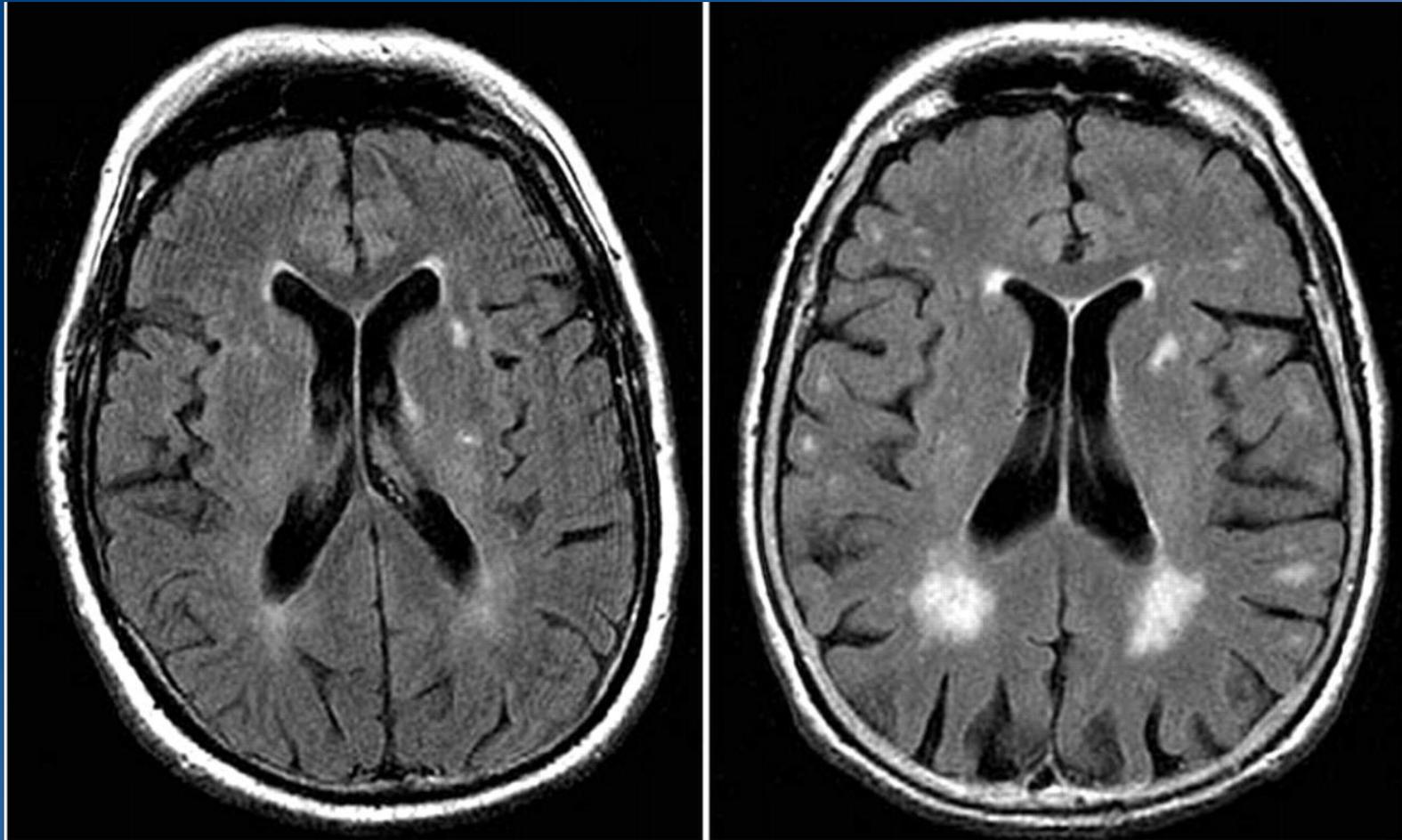
Risk factors for post-stroke VaD:

- ⊙ Older age
- ⊙ Lower education
- ⊙ Recurrent stroke
- ⊙ Left hemisphere stroke
- ⊙ Trouble swallowing, gait changes and urinary incontinence
- ⊙ Acute complications of stroke (seizures, cardiac arrhythmias, aspiration pneumonia etc)

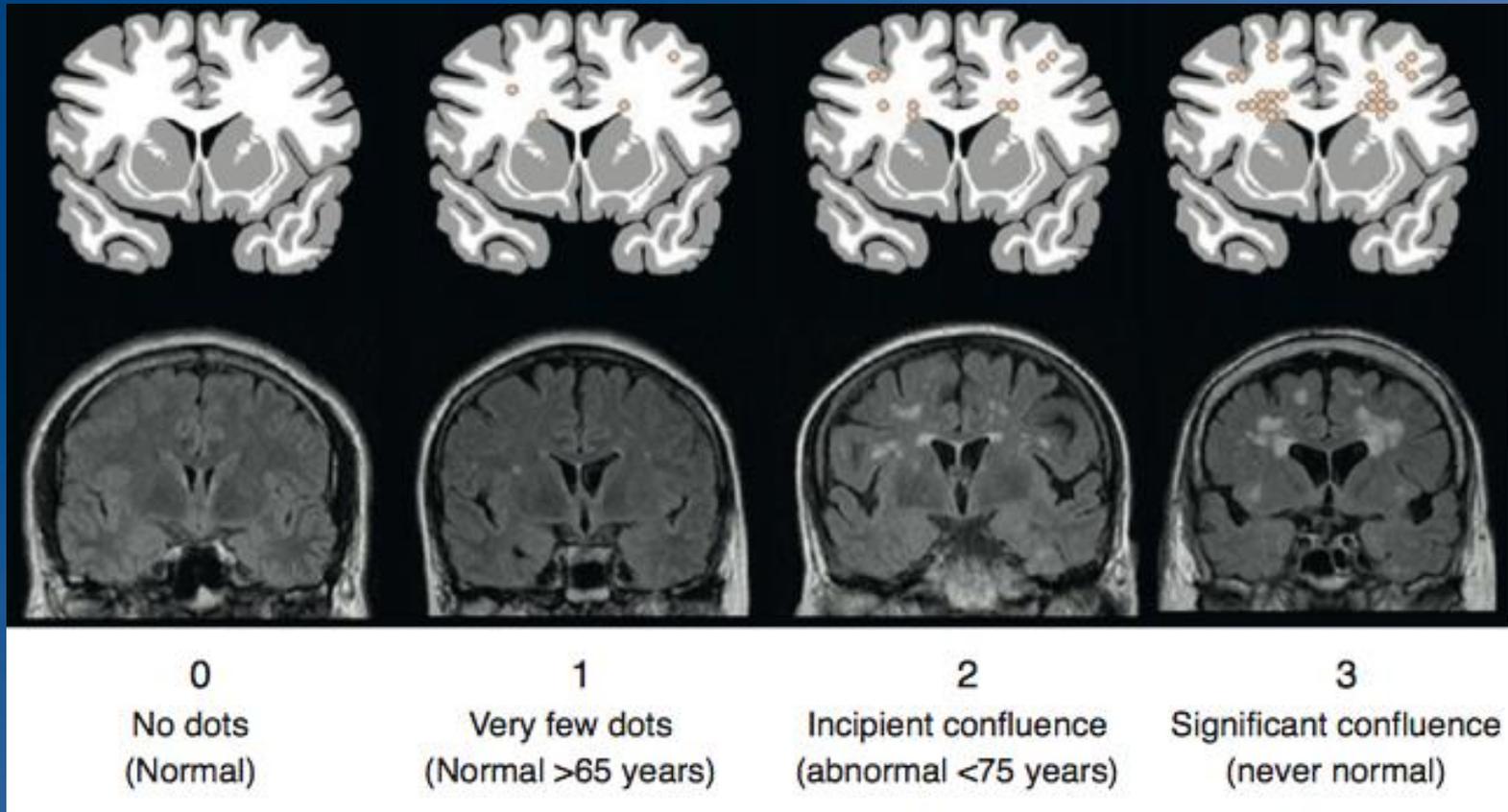
Small Vessel Vascular Dementia

- ⊙ Lead to “sub-cortical Vascular Dementia”
- ⊙ Ischemic lesions secondary to small blood vessel occlusion
- ⊙ Sub-cortical distribution
- ⊙ White matter lesions
- ⊙ Lacunar infarcts

White matter lesions



ARWMC scale for Microvascular disease



Lacunar infarcts

- Lacunar infarcts are small (0.2 to 15 mm in diameter) non-cortical infarcts caused by occlusion of a single penetrating branch of a large cerebral artery
- Most lacunes occur in the basal ganglia (putamen, globus pallidus, thalamus, caudate), subcortical white matter, and pons.

Etiology of lacunar infarcts

- ⦿ Lipohyalinosis of the penetrating arteries is considered the usual cause, particularly of smaller infarcts (3 to 7 mm in length).
- ⦿ Microatheroma of the origin of the penetrating arteries
- ⦿ In some cases, not proven pathologically, tiny emboli have been suspected as the cause of these small infarcts.
- ⦿ Failure of the cerebral arteriolar and capillary endothelium and the associated blood-brain barrier.

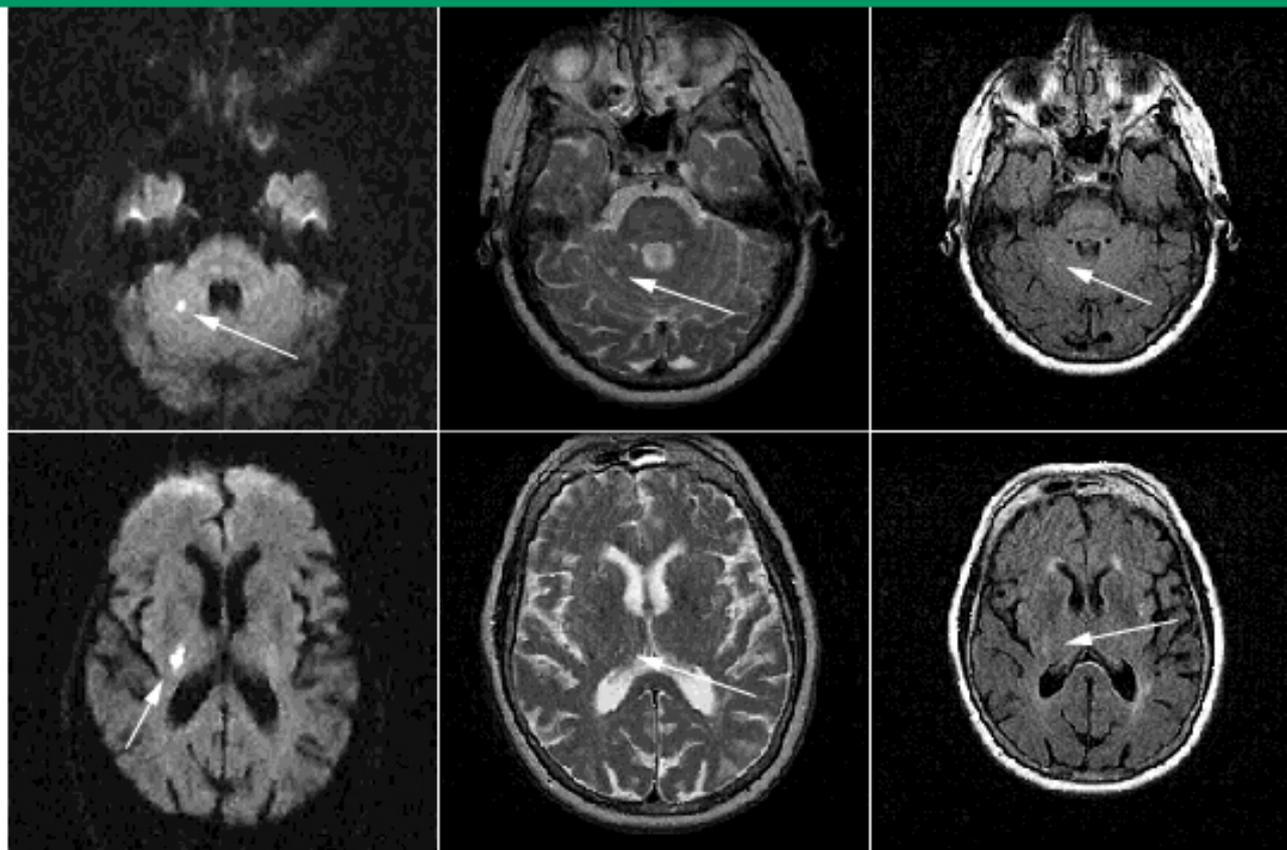
Manifestations of Small Vessel Disease

- Frontal lobe deficits
- Executive dysfunction
- Inattention
- Depressive mood changes
- Changes in gait
- Parkinsonism
- Memory impairment is less pronounced
 - More sub-acute course

Lacunar syndromes

- ◎ More than 20 have been described.
 - Pure motor hemiparesis
 - Pure sensory stroke
 - Ataxic hemiparesis
 - Sensorimotor stroke
 - Dysarthria-clumsy hand syndrome
- ◎ As a general rule, lacunar syndromes lack findings such as aphasia, agnosia, neglect, apraxia, or hemianopsia

Acute lacunar infarction on brain MRI

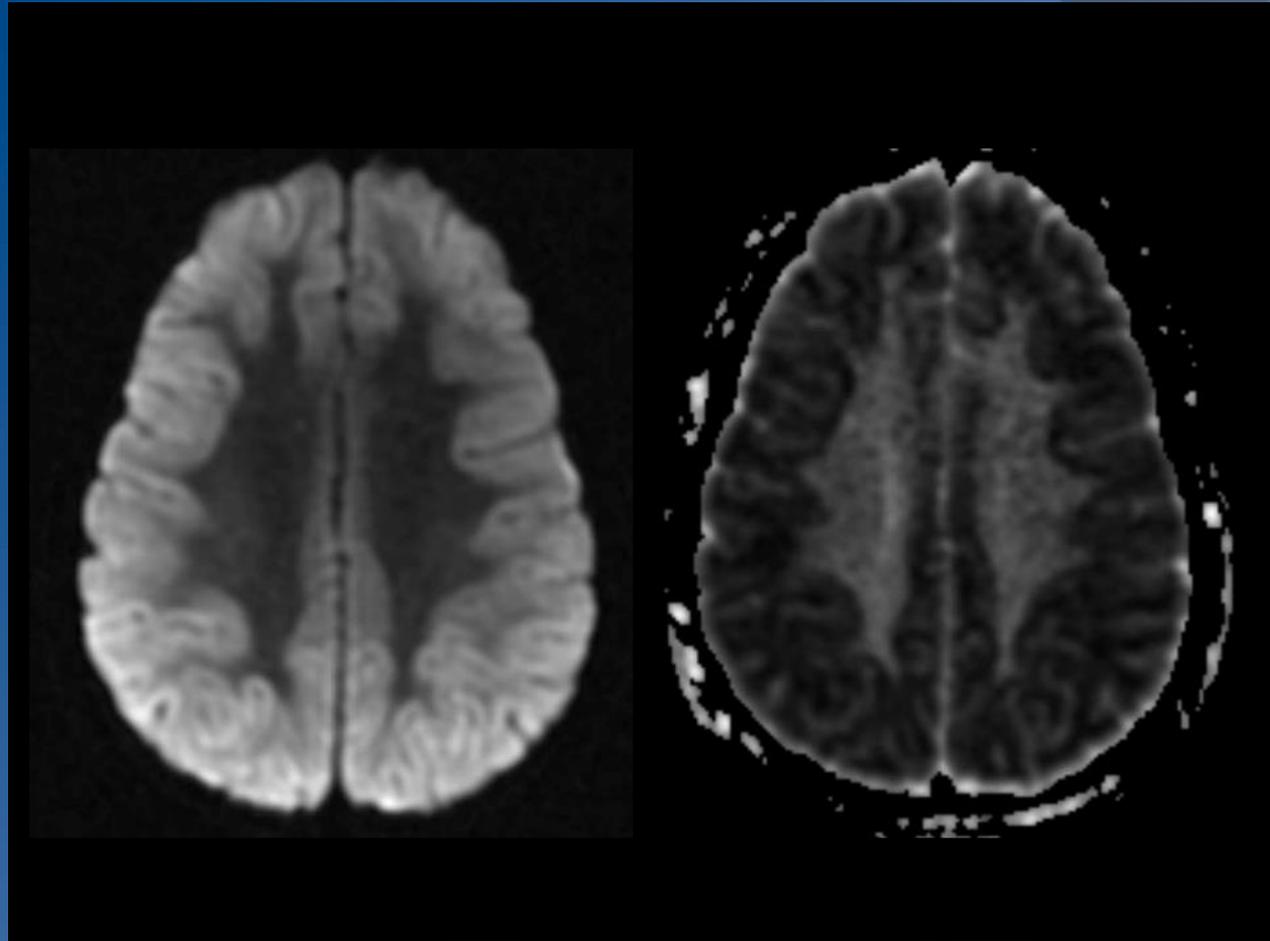


Brain MRI of a 71-year-old woman with a two day history of left-sided ataxic hemiparesis. Left panels: Diffusion-weighted MRI sequences show two acute lesions, one in the cerebellum (top panel) and one in the thalamocapsular region (bottom panel). T2-weighted (middle panels) and FLAIR (right panels) MRI sequences correctly identify the lesions (arrows), but neither could be called "acute" without diffusion imaging. A high-risk cardiac source (an akinetic left ventricular segment) was found on echocardiogram.

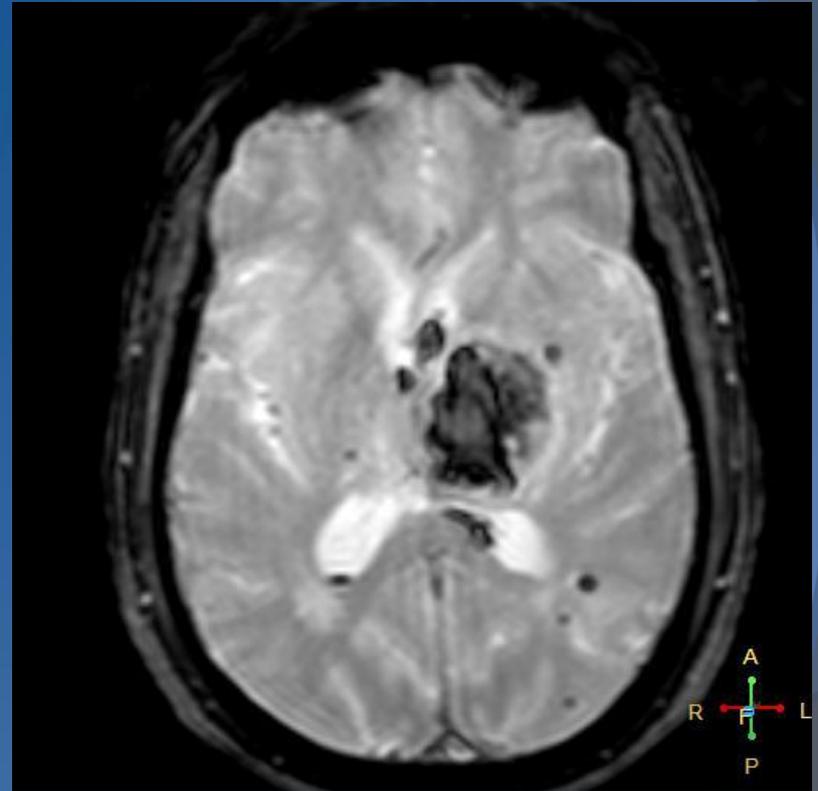
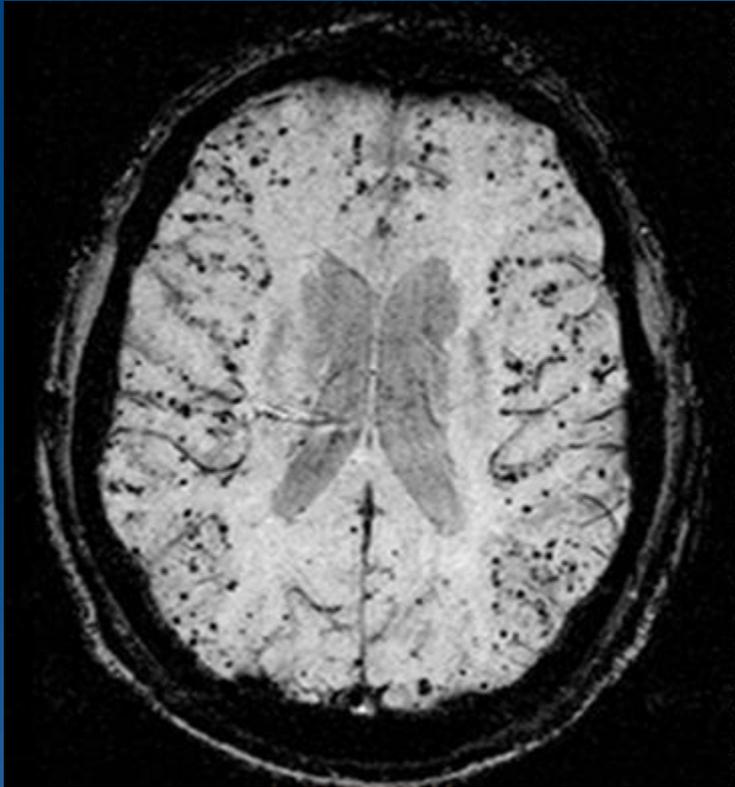
Courtesy of Jarmy Oliveira-Filho, MD.

Ischemic-Hypoxic Vascular Dementia

- ⊙ Anoxia
 - Asphyxia
 - Displaced O₂
 - Depressed respirations
- ⊙ Loss of consciousness



Hemorrhagic dementia



Mixed dementia

- ⦿ Vascular lesions may have synergistic effect with AD pathology
- ⦿ If evidence of cerebrovascular disease present, the density of plaques and tangles needed to cause dementia is lower than that needed for “pure AD”

Risk factors- Small Vessel VaD

- ⊙ Hypertension
- ⊙ Diabetes
- ⊙ Hyperlipidemia
- ⊙ Age
- ⊙ Gender
- ⊙ Race
- ⊙ Hyper-homocysteinuria

Age and VaD

- ⊙ Young onset (< ~45) warrants additional evaluation
- ⊙ Hypercoaguability
 - Genetic factors
- ⊙ Patent Foramen Ovale
- ⊙ Mechanical (vessel tearing, congenital abnormalities)

Diabetes and VaD

- ⦿ Presence of Diabetes approximately doubles the risk of developing VaD
- ⦿ T2DM predisposes to micro- and macrovascular complications throughout the body
- ⦿ T2DM is an established risk factor for cerebral small vessel disease, as well as thrombo-embolic stroke

Diabetes II and VaD

- Relationship Between Baseline Glycemic Control and Cognitive Function in Individuals With Type 2 Diabetes and Other Cardiovascular Risk Factors.(ACCORD-MIND) trial. Tali Cukierman-Yaffe et al. *Diabetes Care* 32:221-226, 2009
 - The study found that a 1% rise in A1c (i.e. from 6.0% to 7.0%) was associated with a significant decline in scores
- Different Patterns of Cerebral Injury in Dementia With or Without Diabetes. Joshua A. Sonnen et al. *Arch Neurol.*2009;66(3):315-322
 - "Individuals without DM but with dementia (DM-/dementia+) had a greater amyloid-beta peptide load and increased levels of F2-isoprostanes in the cerebral cortex, while DM+/dementia+ patients had more microvascular infarcts and an increased cortical IL-6 (interleukin 6) concentration. The number of microvascular infarcts was greater in deep cerebral structures in patients with dementia whose diabetes was treated, whereas amyloid plaque load tended to be greater for untreated diabetic patients with dementia.

Table 2. Population-based prospective studies of diabetes as a risk factor for dementia in older adults.

Source	Study population	Mean age at baseline, yr	Follow-up, yr	Ascertainment of diabetes	Ascertainment of dementia	Covariates	All dementia, RR (95% CI)	Alzheimer's disease, RR (95% CI)	Vascular dementia, RR (95% CI)
Ott et al, 1999 [39]	6370 elderly persons from the community-based Rotterdam Study (Netherlands), 11% with DM	68.9	2.1	Mx, NFG, OGTT	DSM-III (dementia); NINCDS-ADRDA (AD); NINDS-AIREN (VaD)	Age, sex	1.9 (1.3–2.8) *	1.9 (1.2–3.1) *	2.0 (0.7–5.6) *
Luchsinger et al, 2001 [8]	1262 healthy Medicare beneficiaries residing in northern Manhattan (USA), 20% with DM	75.6	4.3	Hx, Mx	DSM-IV (dementia); NINCDS-ADRDA (AD); clinical judgment for stroke-associated dementia (VaD)	Gender, race, education, smoking, hypertension, heart disease, LDL level	NP	1.3 (0.84–1.88)	3.4 (1.70–6.91)
Hassing et al, 2002 [40]	702 elderly individuals from the population-based Origins of Variance in the Old-Old study (OCTO-Twin Study) (Sweden), 15% with DM	83	6–8	Rec, Mx	DSM-III-R (dementia); NINCDS-ADRDA (AD); NINDS-AIREN (VaD)	Age, sex, education, smoking, myocardial infarction, angina, CHF, hypertension, hypotension, TIA, stroke	NP	0.85 (0.36–2.02) [†]	3.63 (1.35–9.76) [‡]
MacKnight et al, 2002 [41]	5574 elderly participants from the Canadian Study of Health and Aging (Canada), 9% with DM	74	5	Hx, Mx, Rec	DSM-III-R (dementia); NINCDS-ADRDA (AD); ICD-10 (VaD)	Age, sex, education, stroke, hypertension, and heart disease	1.26 (0.90–1.76)	1.30 (0.83–2.03)	2.03 (1.15–3.57)
Pella et al, 2002 [42]	2574 Japanese-American elderly men from the fourth exam cohort (1991–1993) of the Honolulu Asia Aging Study (USA), 35% with DM	77	3	Hx, Mx, FG, OGTT	DSM-III-R (dementia); NINCDS-ADRDA (AD); CADDTC (VaD)	Age, education, ApoE epsilon 4 status, diabetes medications, alcohol/smoking status, midlife systolic blood pressure, cholesterol, BMI, ABI, stroke, CHD	1.5 (1.01–2.2)	1.8 (1.1–2.9)	2.3 (1.1–5.0)
Xu et al, 2004 [43]	1301 community elderly dwellers from the Kungsholmen project (Sweden), 8.8% with DM	81	4.7	Rec, Mx, NFG	DSM-III-R (dementia); NINCDS-ADRDA (AD); NINDS-AIREN (VaD)	Age, sex, education, stroke, heart disease, BMI, SBP, DBP, anti-hypertensive medications	1.5 (1.0–2.1)	1.3 (0.9–2.1)	2.6 (1.2–6.1)
Akomolafe et al, 2006 [44]	2210 community-dwelling dementia-free elders from Framingham Study Original cohort (USA), 9.1% with DM	70	12.7	Mx, NFG	DSM-IV (dementia); NINCDS-ADRDA (AD); CADDTC (VaD)	Age, sex, education, plasma homocysteine, SBP, BMI, current smoking, alcohol use, stroke, CVD	1.20 (0.74–1.96)	1.15 (0.65–2.05)	0.81 (0.18–3.70)
Hayden et al, 2006 [45]	3264 aged 65 or older adults from the community-based cohort of Cache County Study of Memory Health and Aging (CCSMHA) (USA), 10.5% with DM	74	3.2	Hx, Mx	DSM-III-R (dementia); NINCDS-ADRDA (AD); NINDS-AIREN (VaD)	Age, sex, education, ApoE epsilon 4 status, hypertension, high cholesterol, obesity, stroke, myocardial infarction, CABG	1.56 (0.90–2.56)	1.33 (0.66–2.46)	2.23 (0.88–5.17) [‡]

*Additional adjustments for education, BMI, alcohol/smoking status, hypertension, ABI, heart disease, stroke did not result in substantial changes of the estimates.

[†]Exclude 81 persons diagnosed with dementia at baseline.

[‡]Diabetes increased the risk of VaD in females after adjustments (aHR 3.33, 95% CI 1.03–9.78) but not males.

ABI indicates ankle-to-brachial index, AD Alzheimer's disease, BMI body mass index, CADDTC California Alzheimer's Disease Diagnostic and Treatment Centers, CHD coronary heart disease, CHF chronic heart failure, DBP diastolic blood pressure, DM diabetes mellitus, FG fasting glucose test, Hx self-report history of diabetes or a physician's diagnosis of diabetes, LDL low density lipoprotein cholesterol, Mx use of anti-diabetes medications including insulin, NFG non-fasting glucose test, NINCDS-ADRDA National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association, NINDS-AIREN National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences, NP not performed, OGTT oral glucose tolerance test, Rec diabetes mellitus ascertained from medical records, RR risk ratio, SBP systolic blood pressure, TIA transient ischemic attack, VaD vascular dementia.

doi:10.1371/journal.pone.0004144.t002

Lu FP, Lin KP, Kuo HK (2009) Diabetes and the Risk of Multi-System Aging Phenotypes: A Systematic Review and Meta-Analysis.

PLoS ONE 4(1): e4144. doi:10.1371/journal.pone.0004144

<http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0004144>

Diabetes II and VaD

- ⊙ An update on type 2 diabetes, vascular dementia and Alzheimer's disease. *Experimental Gerontology*, Vol 47, Issue 11, Nov 2012.
 - T2DM associated with more pronounced vascular pathology
 - T2DM not associated with increased plaque burden
 - Longer duration of T2DM increases risk
 - Glycemic control not as strongly associated
 - Insulin use protective??
- ⊙ More research is needed

Diabetes II and VaD

- Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol.*, 10 (2011), pp. 969–977
 - 2977 patients (mean age 62·5 years; SD 5·8) who had been randomly assigned to treatment groups in the ACCORD study. Our primary cognitive analysis was of patients with a 20-month or 40-month Digit Symbol Substitution Test (DSST) score
 - intensive glycemic control targeting HbA1c to less than 6·0% or a standard strategy targeting HbA1c to 7·0–7·9%
 - 1378 assigned to receive intensive treatment and 1416 assigned to receive standard treatment
 - There was no significant treatment difference in mean 40-month DSST score (difference in mean 0·32, 95% CI –0·28 to 0·91; $p=0·2997$).

Clinical examination

- ◎ Clinician assessment
 - Demographics, family history, cardiac risk factors, medical history, medications
 - Height/weight/waist circumference/BP/timed up and go
 - Exact circumstances surrounding the cognitive and functional impairment
 - Textbook abrupt onset/stepwise decline often not found

HACHINSKI ISCHEMIA SCALE

○ FEATURE	VALUE
• ABRUPT ONSET	2
• STEPWISE DETERIORATION	1
• FLUCTUATING COURSE	2
• NOCTURNAL CONFUSION	1
• RELATIVE PRESERVATION OF PERSONALITY	1
• DEPRESSION	1
• SOMATIC COMPLAINTS	1
• EMOTIONAL INCONTINENCE	1
• HISTORY/PRESENCE OF HYPERTENSION	1
• HISTORY OF STROKES	2
• EVIDENCE OF ARTEROSCLEROSIS	1
• FOCAL NEUROLOGICAL SYMPTOMS	2
• FOCAL NEUROLOGICAL SIGNS	2

○ SCORES OVER 7 SUGGEST A VASCULAR ETIOLOGY

Prevention of VaD

- Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet Vol 352, No 9137. p1347–1351, 24 October 1998
 - In elderly people with isolated systolic hypertension, antihypertensive treatment was associated with a lower incidence of dementia. If 1000 hypertensive patients were treated with antihypertensive drugs for 5 years 19 cases of dementia might be prevented.

Treatments for VaD

- ◎ Primary intervention is management of cerebrovascular risk factors.
- ◎ There are as yet no diabetes-specific treatments with proven efficacy in preventing or ameliorating cognitive decline.
- ◎ Anti-platelet agents with mixed results

Once VaD is present,

- Acetyl cholinesterase inhibitors (AChEI) – may have mild - moderate benefit, patients with VaD are more likely to experience side effects with AChEI than AD patients and so may be more likely to discontinue the drug
- Memantine – may be useful as an adjunct to AChEI in patients with moderate to severe dementia, not covered by Pharmacare
- Anti depressants (specifically SSRIs)
- Atypical antipsychotics

AAN Practice Guidelines

- There are no adequately controlled trials demonstrating pharmacologic efficacy for any agent in ischemic vascular (multi-infarct) dementia.

Take Home Messages

- ⊙ VaD is a common cause of dementia
- ⊙ Look for risk factors of VaD and focal neurological signs
 - Especially Hypertension!
 - Prevention is the best management
- ⊙ Clinical Pearls
 - Significant memory impairment is not always present
 - Do a cognitive screening test
 - (complaint does not equal deficit!)
- ⊙ Early referral to a comprehensive diagnostic center is appropriate
 - Center for Alzheimer's Care, Imaging, and Research at the University of Utah

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