VCI—Diagnosis and Neuropathological features

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Prof Raj N Kalaria, DSc (Med), FRCP..FMedSci
Translational and Clinical Research Institute
Newcastle University
Campus for Ageing and Vitality, Newcastle upon Tyne NE4 5PL, UK
Email: raj.kalaria@newcastle.ac.uk

MRC Medical Research Council

COGFAST Memory After Stroke Study

VCI and Cerebral Vascular Diseases

Plan

- Introduction, Definitions, Stroke as substrate of VCI/Dementia
- VCING: Small vessels – Arteriolosclerosis, Atherosclerotic lesions vs Small vessel disease pathologies
- Cerebral Amyloid Angiopathy and Rarer CVDs, SVDs
- CogFAST: Vascular pathology and Dementia
- Mechanisms and Diagnostic considerations

Consequences of Cerebrovascular Disease and Stroke Pathology

Some changes can be clinically covert and pathologically difficult to interpret

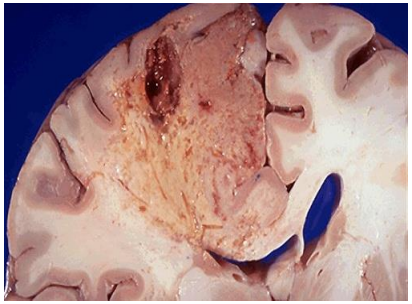
Changes in Tissue:

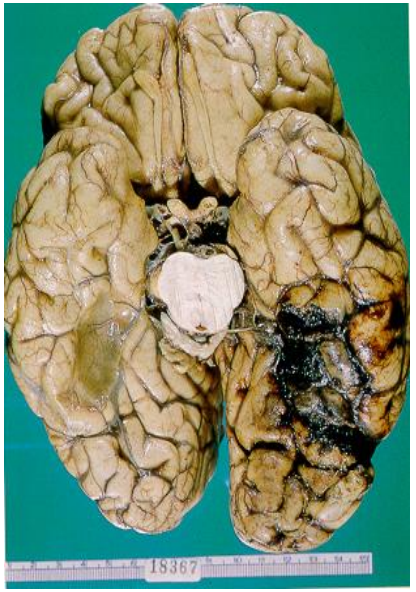
- Infarct(s)- large, small and microinfarction
- Leukoencephalopathy- WM myelin loss, axonal damage

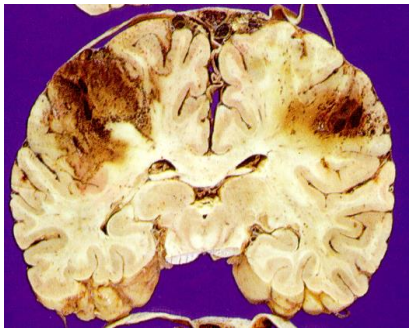
Vascular changes

- Atherosclerosis and arteriolosclerosis (± hereditary)
- Hypertensive disease- vascular distortion, coiling, kinking, twisting
- Cerebral amyloid or protein angiopathies and Intracerebral Haemorrhage
- Arteritis - giant cell arteritis, Takayasu disease
- Vasculitis -primary angiitis, Tuberculosis, bacterial and fungal
- Aneurysms- sacular, berry, fusifom, cerebral
- Vascular malformations- cavernous hemiangioma, arteriovenous, capillary telelengactisias

Common Pathological lesions in CVD – Neuropathology reporting



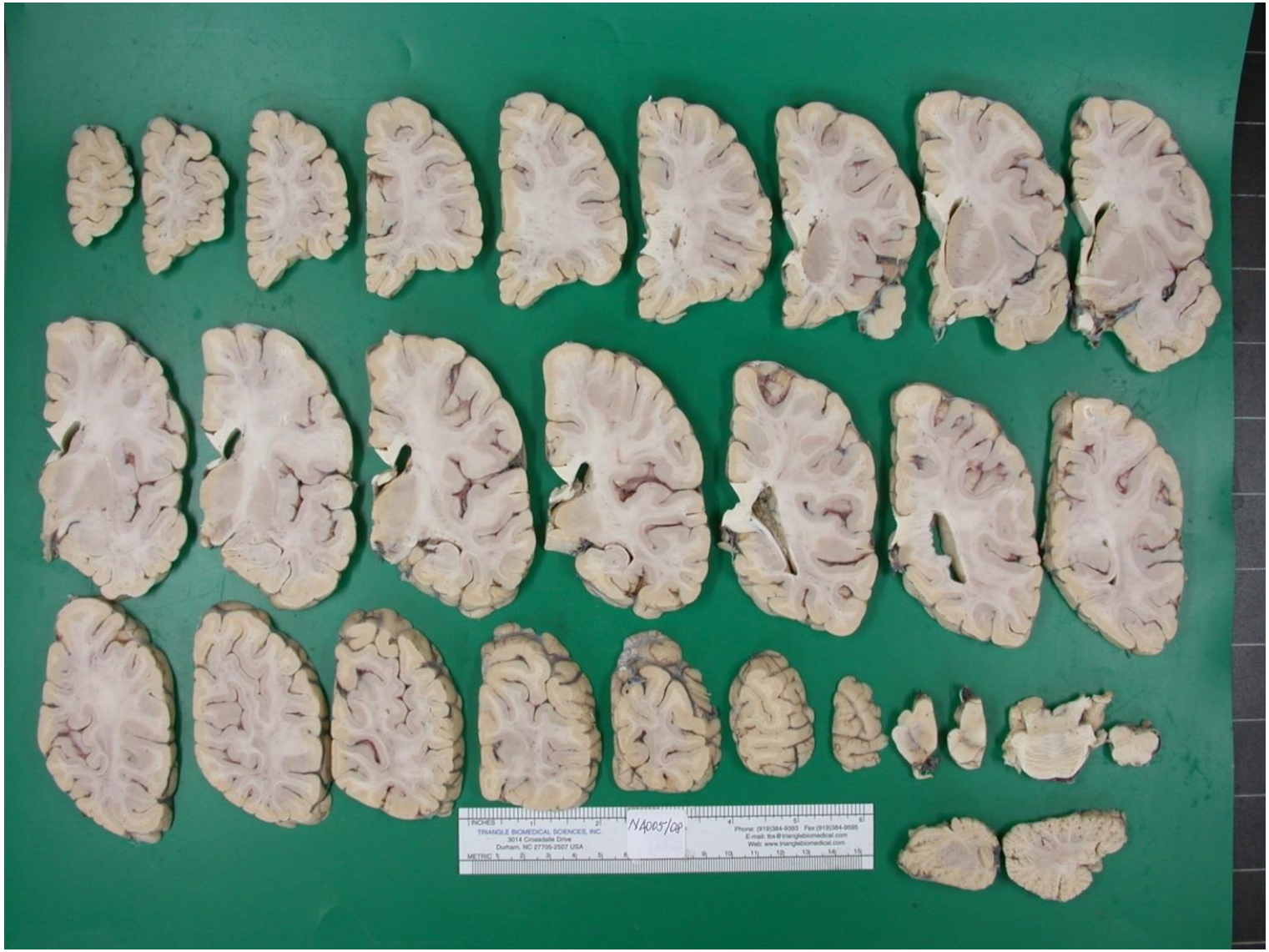




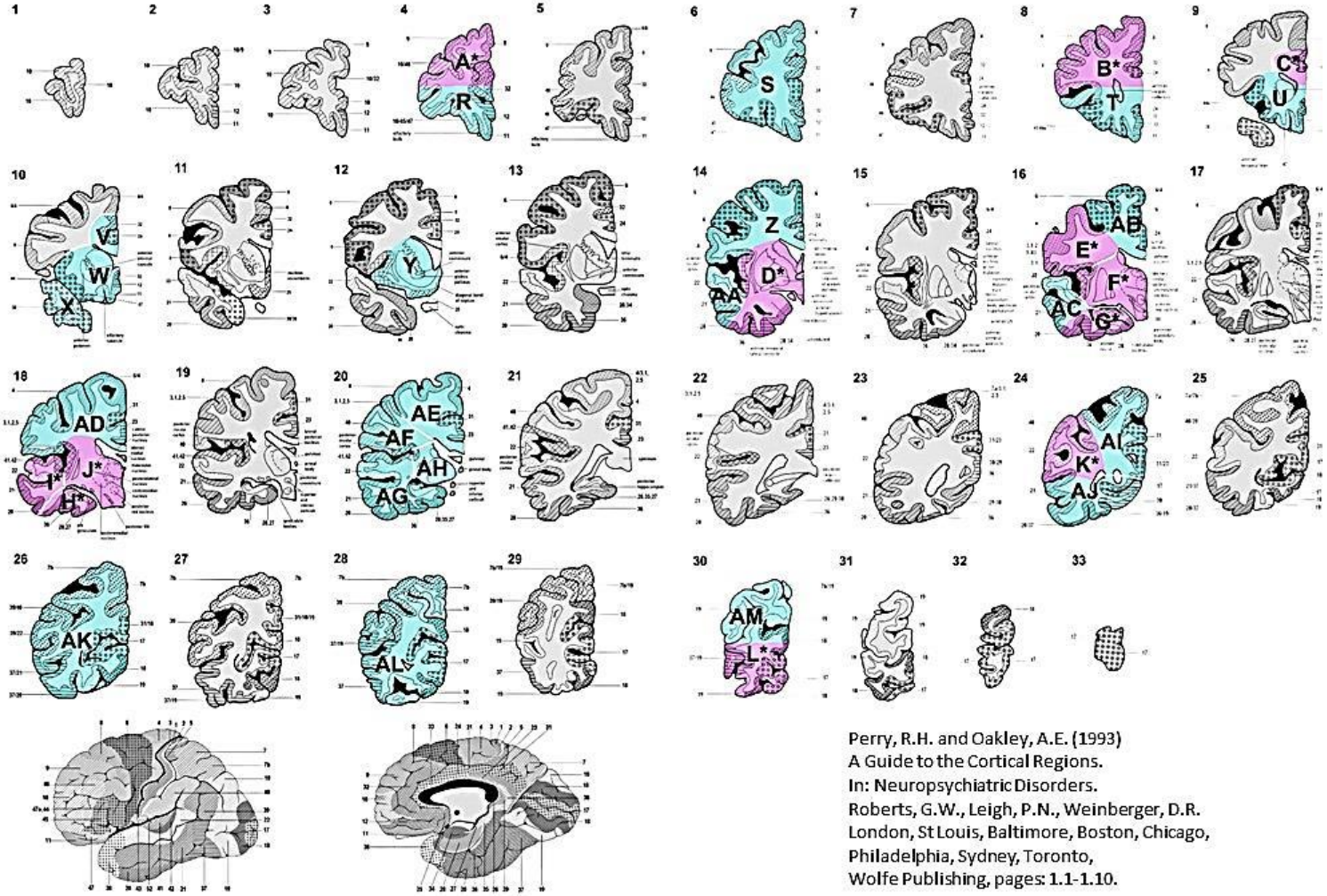
Key features for pathological diagnosis:

- Ischaemic or haemorhagic infarct(s)
- Location: cortex, WM, basal ganglia, brainstem (pontine), cerebellum
- Circulation involved: arterial territories- anterior, middle or posterior
- Laterality: right or left anterior and posterior
- Sizes / number of infarcts = dimension: 0-4 mm, 5-15 mm, 16-30mm, 31>50mm
- Microinfarction; <5mm determine as small or microinfarcts.
- Lacunes and lacunar infarcts: etat lacunaire and etat crible (gray and WM)
- Small vessel disease: lipohyalinosis; fibroid necrosis; CAA
- Leukoencephalopathy (WMD): ant vs post; pv vs d WM; rarefaction/ incomplete
- Degree of gliosis: mild, moderate or severe
- Alzheimer pathology (NFT, neuritic plq staging). >stage III = mixed AD and VaD

Routine Sampling and Reporting

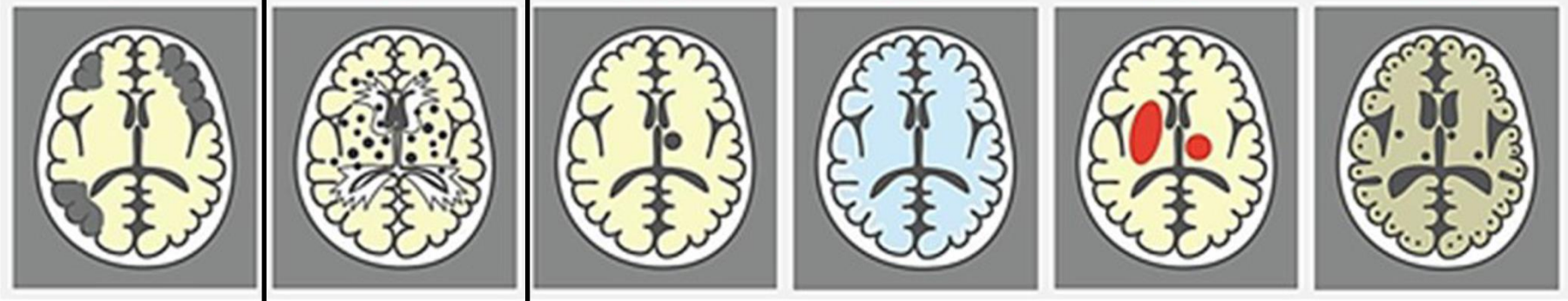


Newcastle Brain Map
Diagnostic Samples/“Blocks”



Perry, R.H. and Oakley, A.E. (1993)
A Guide to the Cortical Regions.
In: Neuropsychiatric Disorders.
Roberts, G.W., Leigh, P.N., Weinberger, D.R.
London, St Louis, Baltimore, Boston, Chicago,
Philadelphia, Sydney, Toronto,
Wolfe Publishing, pages: 1.1-1.10.

Newcastle Categorization of the Major CV lesions Associated with Cognitive Impairment



I	II	III	IV	V	VI
Large infarcts or cortical infarcts	Multiple small or lacunes	Strategic infarcts / lacunes	Hypoperfusive lesions, HS	Cerebral haemorraghes	CVD pathology with AD
LVD; atherosclerosis	SVD; micro-vascular changes	Embolic/ hyper-tensive disease	Cardiac arrest	Different angiopathies	Stroke injury and ageing-related AD
Focal signs, stepwise progression	No or slight focal signs, insidious progression	Focal signs, stepwise progression	Absence of focal signs, insidious progression	Focal signs, stepwise progression	Absence of focal signs, insidious progression
MID or cortical VaD	SVID	Strategic infarct dementia	VCI or VaD	VCI or dementia with CH	VaD with AD pathology

Slide courtesy of Dr Ken Nagata

Kalaria, RN, et al. J Neuro Sci 226: 75-80, 2004

Two Major Categories of CVD: Implications for VCI-Dementia

(simplified version of Oxford Community Stroke Project (OCSP) classification)

Large-vessel disease

(Basal brain arteries, >1 mm diam)

Cardiac embolic events

Atherosclerosis, plaque rupture, intraplaque hemorrhage, thrombotic occlusion, and embolism, dissection, dolichoectasia

→ **Large cortical and subcortical infarcts**

Familial traits, several gene polymorphisms

Small-vessel disease

(Intracerebral vessels; <1mm diam)

Arteriolosclerosis, Fibrinoid necrosis, Microaneurysm, Fibrohyalinosis, Microatheroma. Cerebral amyloid angiopathy, Segmental arterial disorganization, telangiectasis

Imaging definitions: leukoariaosis (WMHs), lacunar infarcts, CMBs, PVS

→ **Small subcortical; cortical infarcts**

(<1.5 cm)

→ **Diffuse white matter changes**

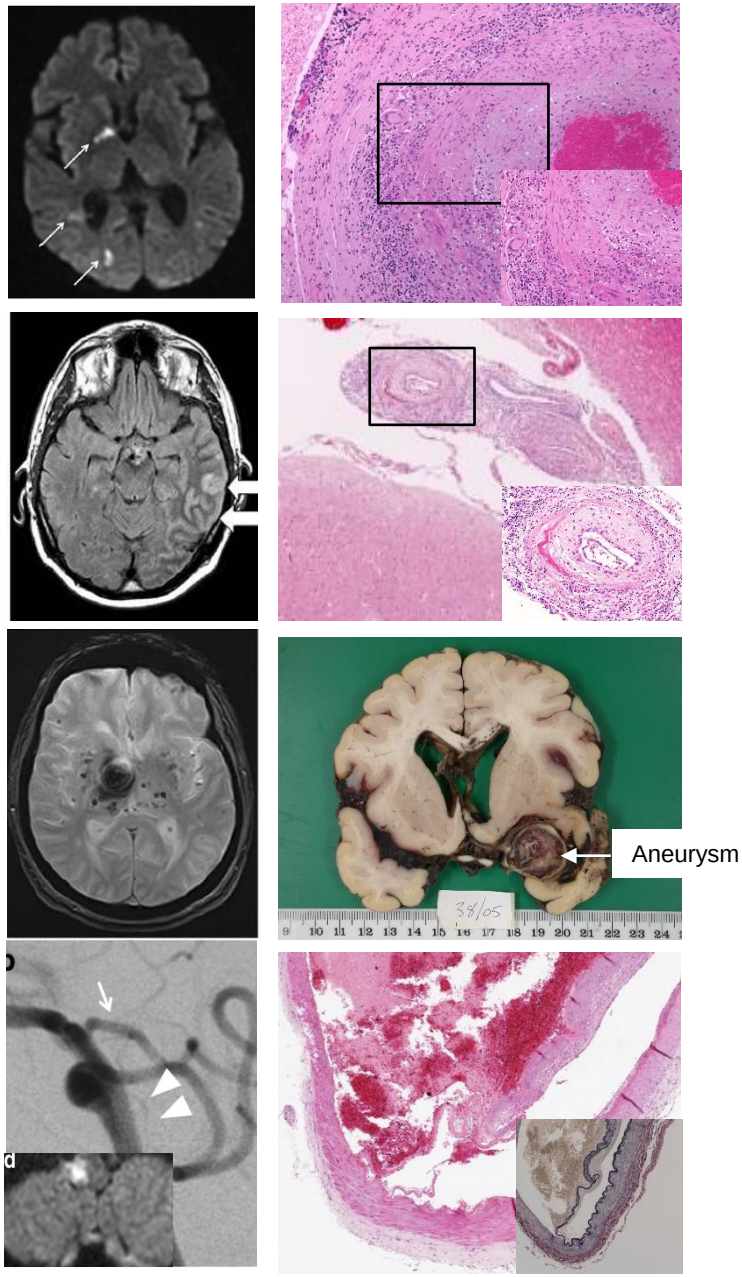
Hereditary forms (e.g CADASIL, gene polymorphisms

Rarer consequences of CVDs

~2-5% total CVDs; 5-10% CVA, control risk, biopsy

- Arteritis - ***giant cell arteritis*** *(GCA), Takayasu disease*
- Vasculitis ***-primary angiitis*** *(PACNS), Tuberculosis, bacterial and fungal*
- Aneurysms- *sacular, berry, fusifom,* ***Intracerebral***
- Arterial Dissections- *carotid,* ***vertebral-basilar***

- Vascular malformations- *cavernous hemiangioma, AVMs, capillary telelengactisias*



From Kalaria R et al, Greenfield's, 2015; 2016

Staging and natural history of cerebrovascular pathology in dementia

Deramecourt V et al, 2012

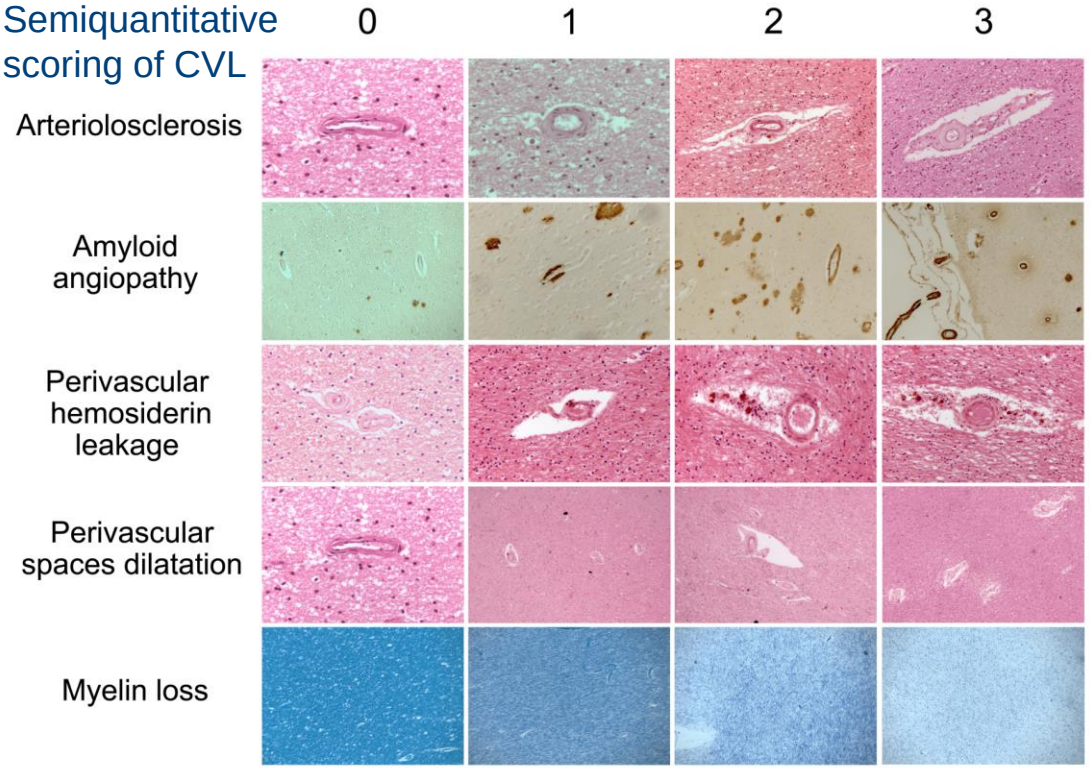
V. Deramecourt, MD, PhD
J.Y. Slade, BSc
A.E. Oakley, MBiol
R.H. Perry, FRCPath
P.G. Ince, FRCPath
C.-A. Maurage, MD, PhD
R.N. Kalaria, FRCPath

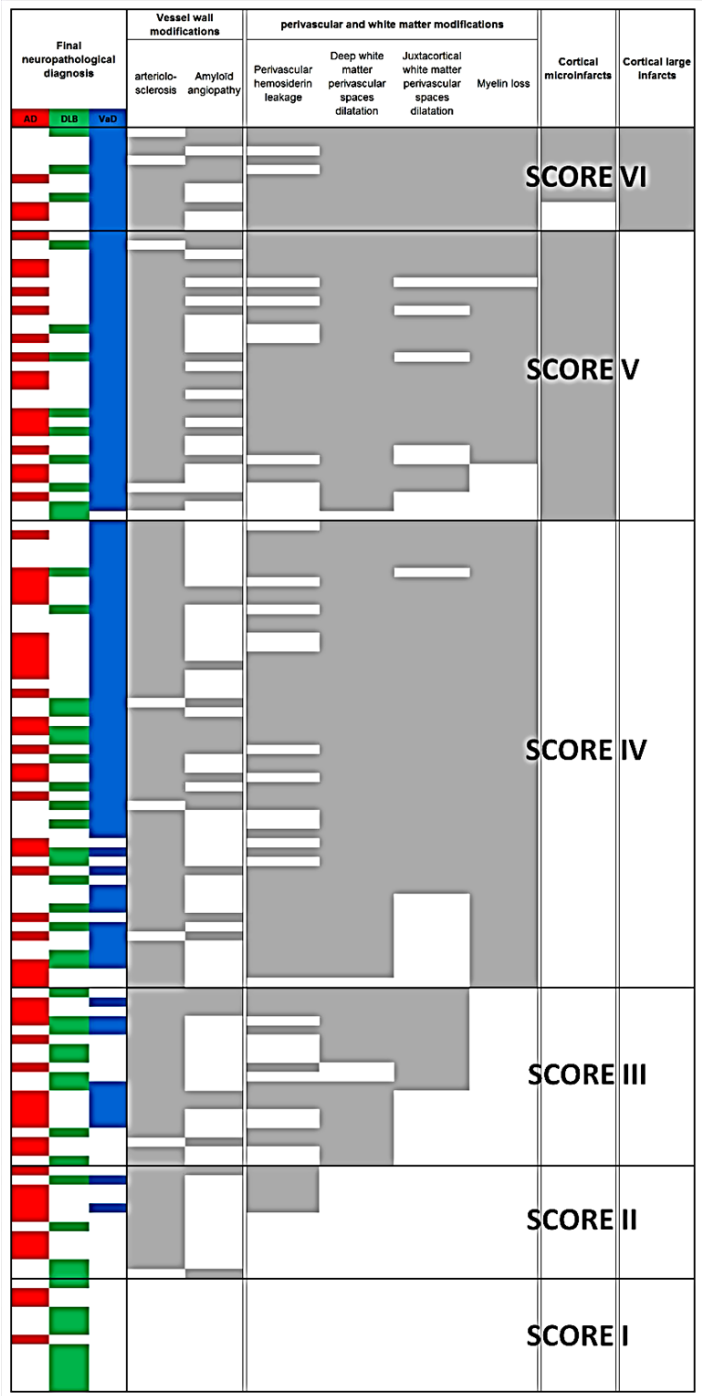
ABSTRACT

Objective: Most pathologic studies indicate that significant vascular changes are found in the majority of elderly persons, either alone or in association with neurodegenerative processes such as Alzheimer disease (AD) or dementia with Lewy bodies (DLB). Cumulative burden of cerebrovascular lesions can explain cognitive decline described as vascular cognitive impairment, but because there is a lack of consensus in the best way to quantify vascular pathology, the relationship between cognitive decline and cerebrovascular disease remains uncertain. We developed a rating scheme for cerebrovascular lesions using postmortem brains from patients with dementia from 2 European tertiary care memory clinics.

Staging and Natural history of cerebrovascular pathology (SVD)

Semiquantitative scoring of CVL





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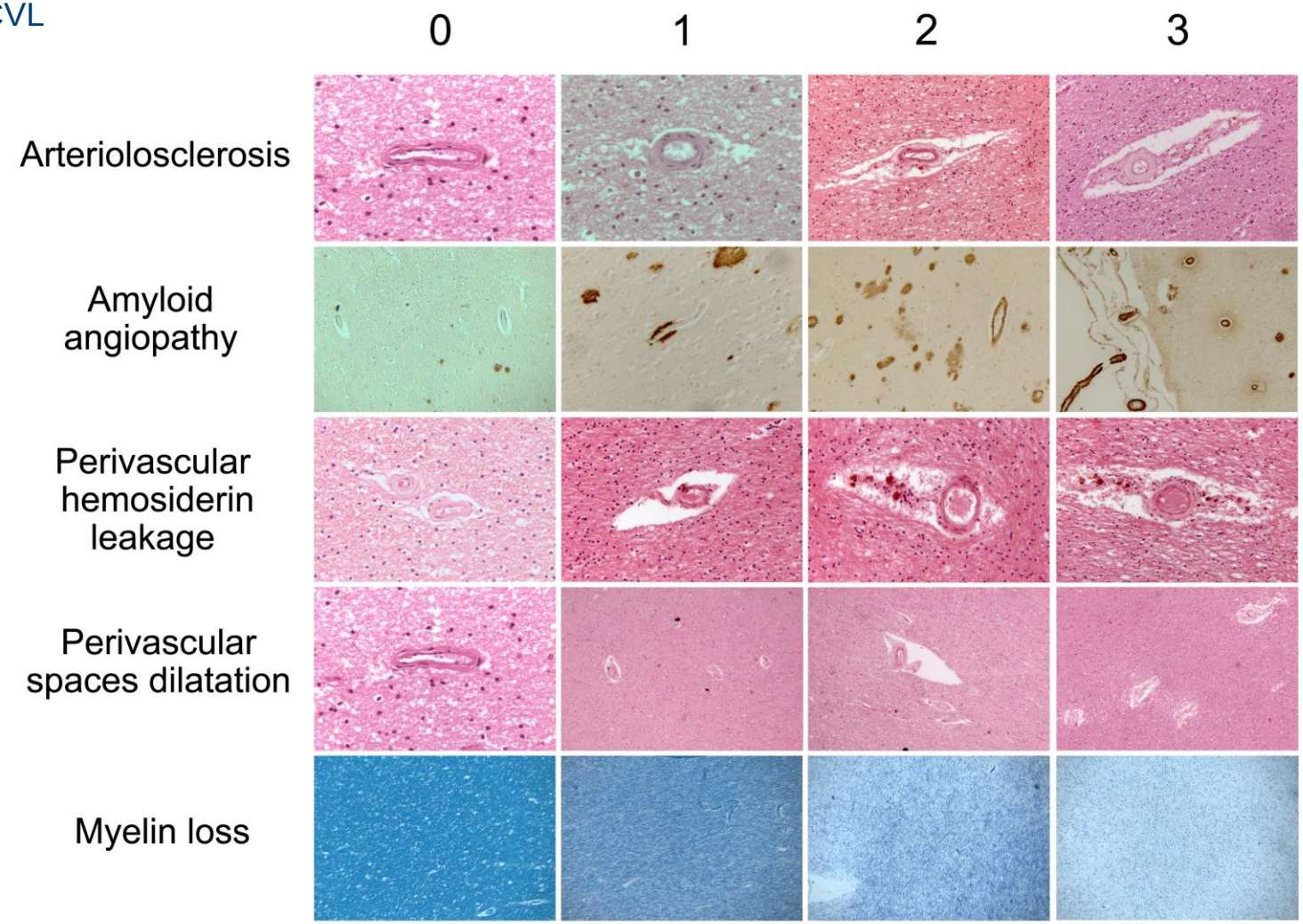
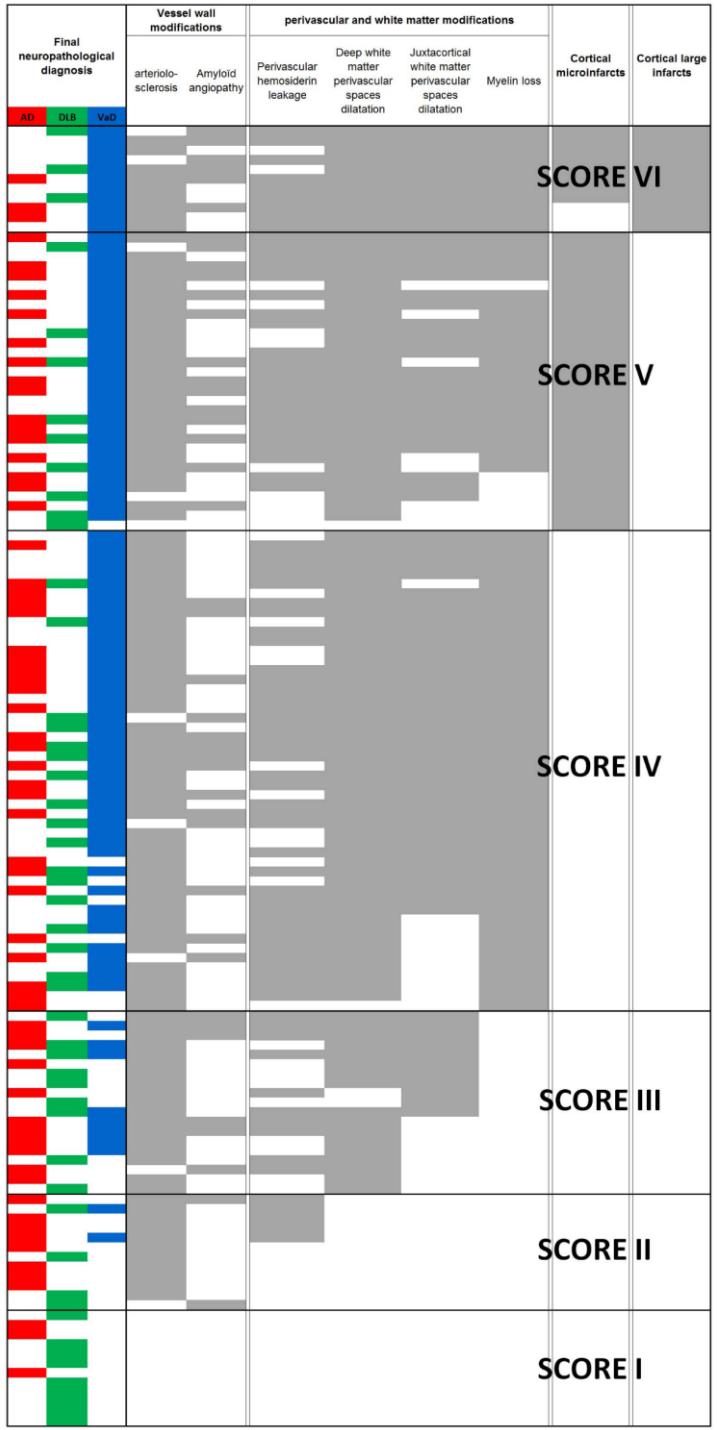


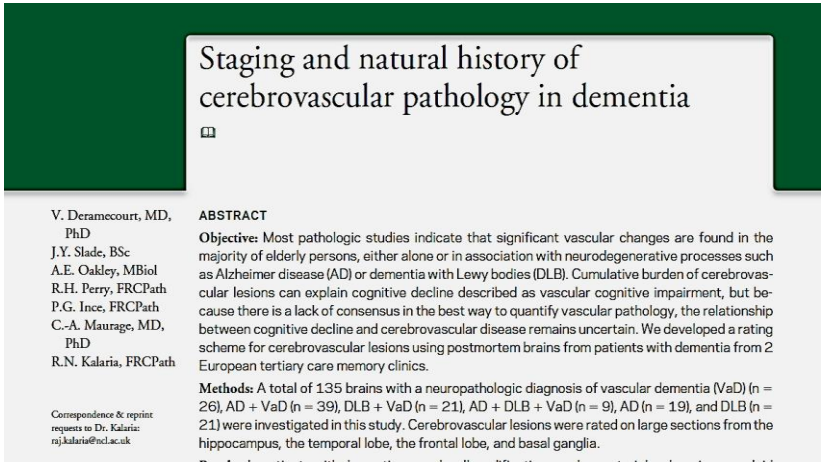
Deramecourt V et al, 2012

Frontal and Temporal lobes	
Stage 0	Normal appearance of brain vessel, white matter and cortex
Stage I	Mild modification of vessel walls, perivascular spaces or white matter
Stage II	Moderate to severe but isolated modification of the vessel walls (arteriolosclerosis or amyloid angiopathy), usually associated with haemosiderin deposits in the perivascular spaces
Stage III	Moderate to severe perivascular space dilatations either in the deep or the juxtacortical white matter
Stage IV	Moderate to severe myelin loss
Stage V	Presence of cortical microinfarcts
Stage VI	Presence of large infarcts
Hippocampus	
Stage 0	Normal appearance
Stage I	Mild modification of vessel walls or perivascular spaces
Stage II	Moderate to severe perivascular space dilatations
Stage III	Presence of microinfarcts (usually in the Amon's horn or the subiculum)
Stage IV	Presence of large infarcts
Basal ganglia	
Stage 0	Normal appearance
Stage I	Mild modification of vessel walls or perivascular spaces
Stage II	Moderate to severe perivascular space dilatations
Stage III	Presence of microinfarcts
Stage IV	Presence of large infarcts
Total vascular score: Fx+Tx+Hx+Bx (/20)	



Deramecourt V et al, 2012

Staging and Natural History of cerebrovascular pathology in Dementia: Key Points



Staging and natural history of cerebrovascular pathology in dementia

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Correspondence & reprint requests to Dr. Kalaria: raj.kalaria@ncl.ac.uk

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Objective: Most pathologic studies indicate that significant vascular changes are found in the majority of elderly persons, either alone or in association with neurodegenerative processes such as Alzheimer disease (AD) or dementia with Lewy bodies (DLB). Cumulative burden of cerebrovascular lesions can explain cognitive decline described as vascular cognitive impairment, but because there is a lack of consensus in the best way to quantify vascular pathology, the relationship between cognitive decline and cerebrovascular disease remains uncertain. We developed a rating scheme for cerebrovascular lesions using postmortem brains from patients with dementia from 2 European tertiary care memory clinics.

Methods: A total of 135 brains with a neuropathologic diagnosis of vascular dementia (VaD) (n = 26), AD + VaD (n = 39), DLB + VaD (n = 21), AD + DLB + VaD (n = 9), AD (n = 19), and DLB (n = 21) were investigated in this study. Cerebrovascular lesions were rated on large sections from the hippocampus, the temporal lobe, the frontal lobe, and basal ganglia.

- **SV modifications: *arteriolosclerosis or amyloid angiopathy* - most common and earliest changes; followed by perivascular spacing**

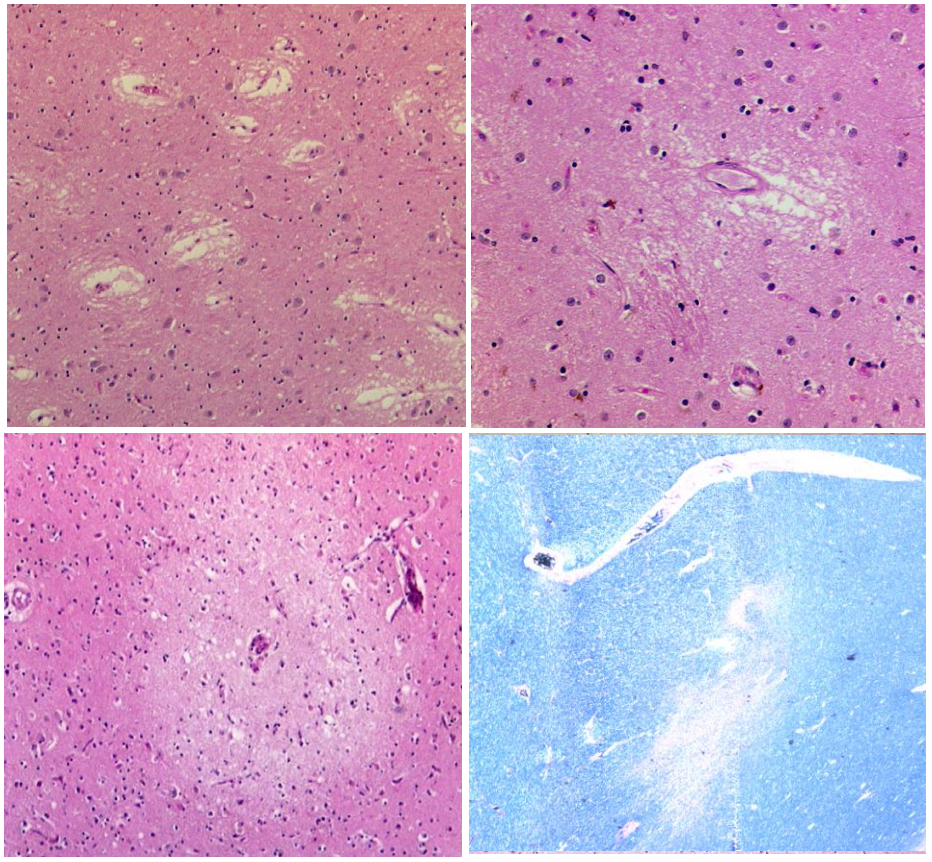
- Lacunar or regional microinfarcts infarcts, consequences of independent processes

- Total scores for vascular pathology: VaD > **AD** > DLB > controls

- Predicted Regional progression: Frontal > temporal lobe $\geq$ basal ganglia

Deramecourt V et al, Neurology, 2012; cf. Blevins et al, 2020

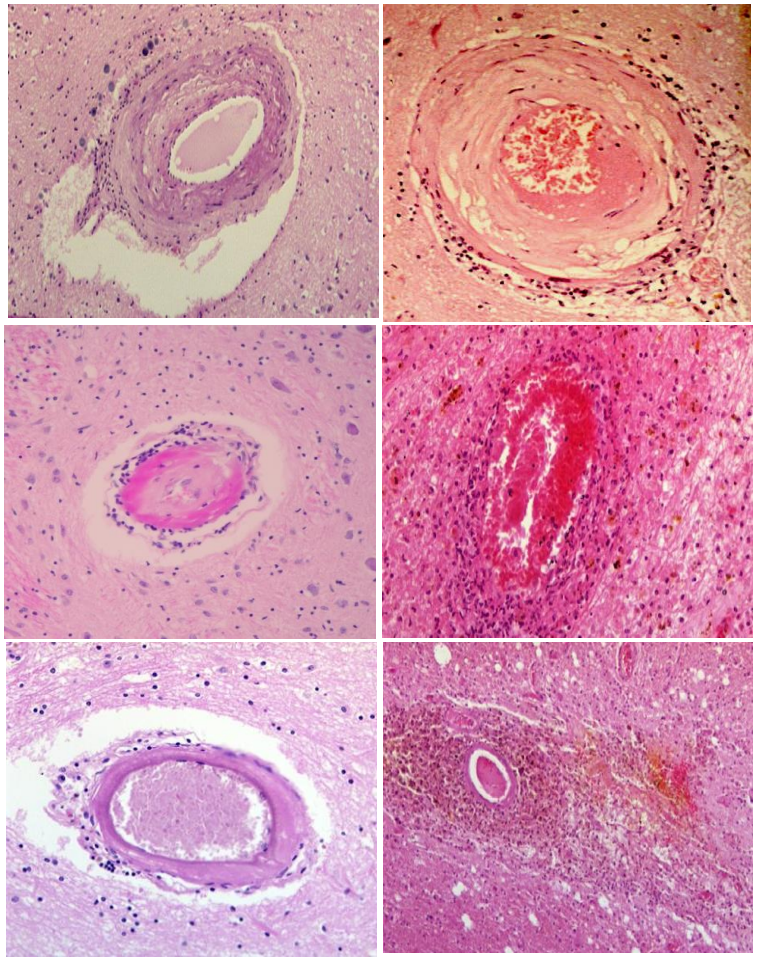
Microinfarcts important substrate of SVD



Microinfarcts

- Defined as microscopic (<5 mm diameter; 50-500um)
- multiple
- +/- involve vessels
- Subcortical and cortical (e.g. CAA related)

SVD: Structural and Functional Changes



Range of diameters <1mm- 20μm plus capillaries

- Loss of VSMCs in media (*arteriolosclerosis*)
- Fibroid necrosis
- Hyalinzation and Collagenosis
- Thickening of BM
- Increase in initima
- Endothelial damage
- Obliteration and occlusion
- Tortuosity, coiling

BBB changes
Perivascular cell changes
Increased resistance
Decreased autoregulation

Kalaria, 2016; Blevins et al, 2020

VCING Criteria 2016

doi: 10.1093/brain/aww214 BRAIN 2016: 139; 2957–2969 | 2957
BRAIN
A JOURNAL OF NEUROLOGY

Vascular cognitive impairment neuropathology guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment

Olivia A. Skrobot,[1] Johannes Attems,[2] Margaret Esiri,[3] Tibor Hortobágyi,[4,5] James W. Ironside,[6] Rajesh N. Kalaria,[2] Andrew King,[7] George A. Lammie,[8] David Mann,[9] James Neal,[10] Yoav Ben-Shlomo,[11] Patrick G. Kehoe[1] and Seth Love[1]

Seven pathologies: Leptomeningeal CAA, large infarcts, lacunar infarcts, microinfarcts, arteriolosclerosis, perivascular space dilation and myelin loss predicted cognitive impairment.

The preferred multivariable logistic regression moderate/severe occipital leptomeningeal CAA, moderate/severe arteriolosclerosis in occipital WM, and at least one large infarct (77%). Presence of 0, 1, 2 or 3 of these features = predicted probabilities of VCI of 16%, 43%, 73% or 95%, respectively.

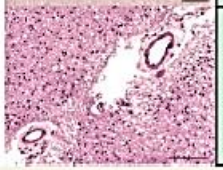
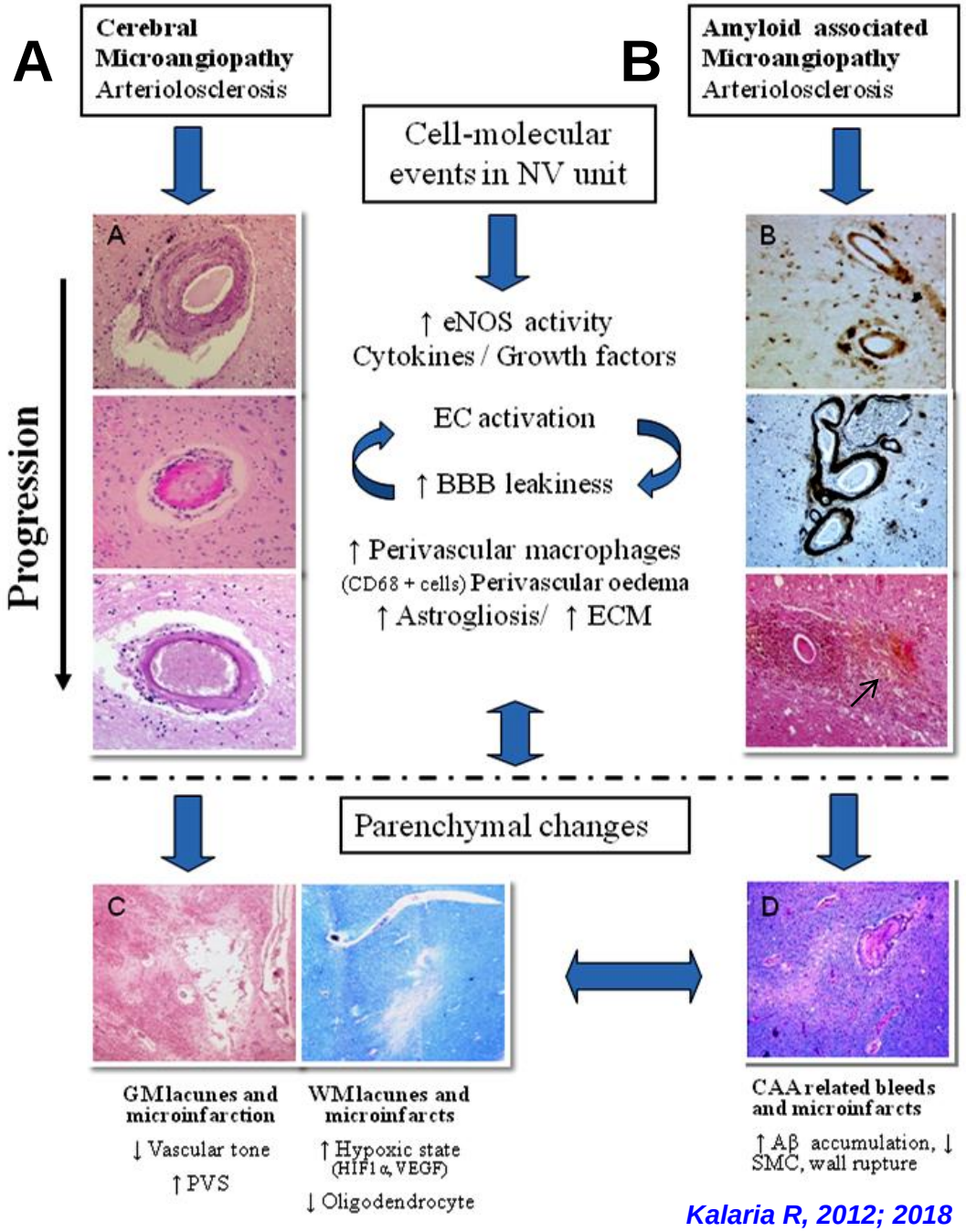
Likelihood that cerebral vascular disease contributed to cognitive impairment		Low (<50%)			Moderate (50-80%)		High (>80%)		
One or more large (> 10 mm) subcortical cerebral infarcts		-	-	-	+	-	+	+	+
Moderate or severe occipital leptomeningeal CAA		-	+	-	-	+	+	-	+
Moderate or severe occipital white matter arteriolosclerosis		-	-	+	-	+	-	+	+

Figure 1 VCING model estimating the likelihood that cerebrovascular disease contributed to cognitive impairment. Combinations of the three main determinants—at least one large (>10 mm diameter) infarct, moderate/severe occipital leptomeningeal CAA, and moderate/severe arteriolosclerosis in the occipital white matter—are used to assign a low, intermediate or high likelihood that cerebrovascular disease contributed to cognitive impairment in an individual case. Scale bars in the *top*, *middle* and *bottom* photomicrographs represent 1 mm, 250 µm and 100 µm, respectively.

Vascular cognitive impairment neuropathology guidelines (VCING)

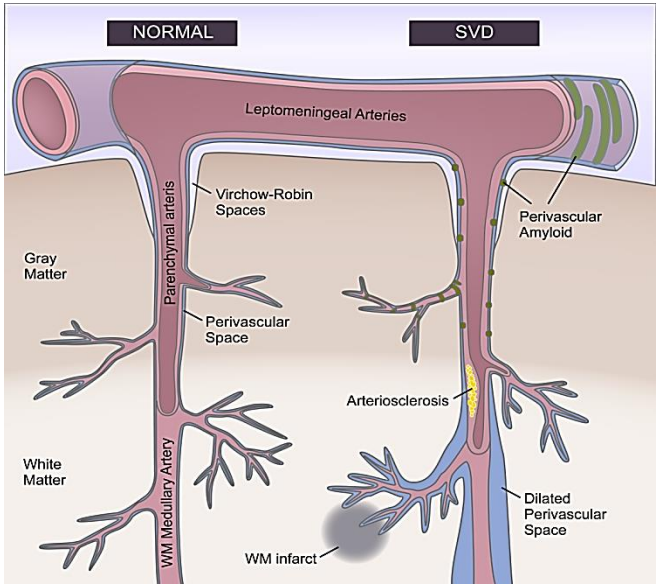
- Blinded post-mortem assessment from 55-100 years olds
- No significant neurodegenerative disease
- Formal cognitive assessments within 12 months of death
- Fourteen different vessel and parenchymal pathologies assessed in 13 brain regions
- Variability in assessment of the severity of arteriolosclerosis (0.45–0.91) and microinfarcts (0.52–0.84)
- Seven pathologies—leptomeningeal CAA, large infarcts, lacunar infarcts, microinfarcts, arteriolosclerosis, PVS dilation and myelin loss—predicted cognitive impairment;
- ***Moderate/severe arteriolosclerosis, CAA and at least one large infarct predicted VCI (95%)***



Kalaria R, 2012; 2018

Ageing related Vascular disease

(hypertension, diabetes, atherosclerosis)



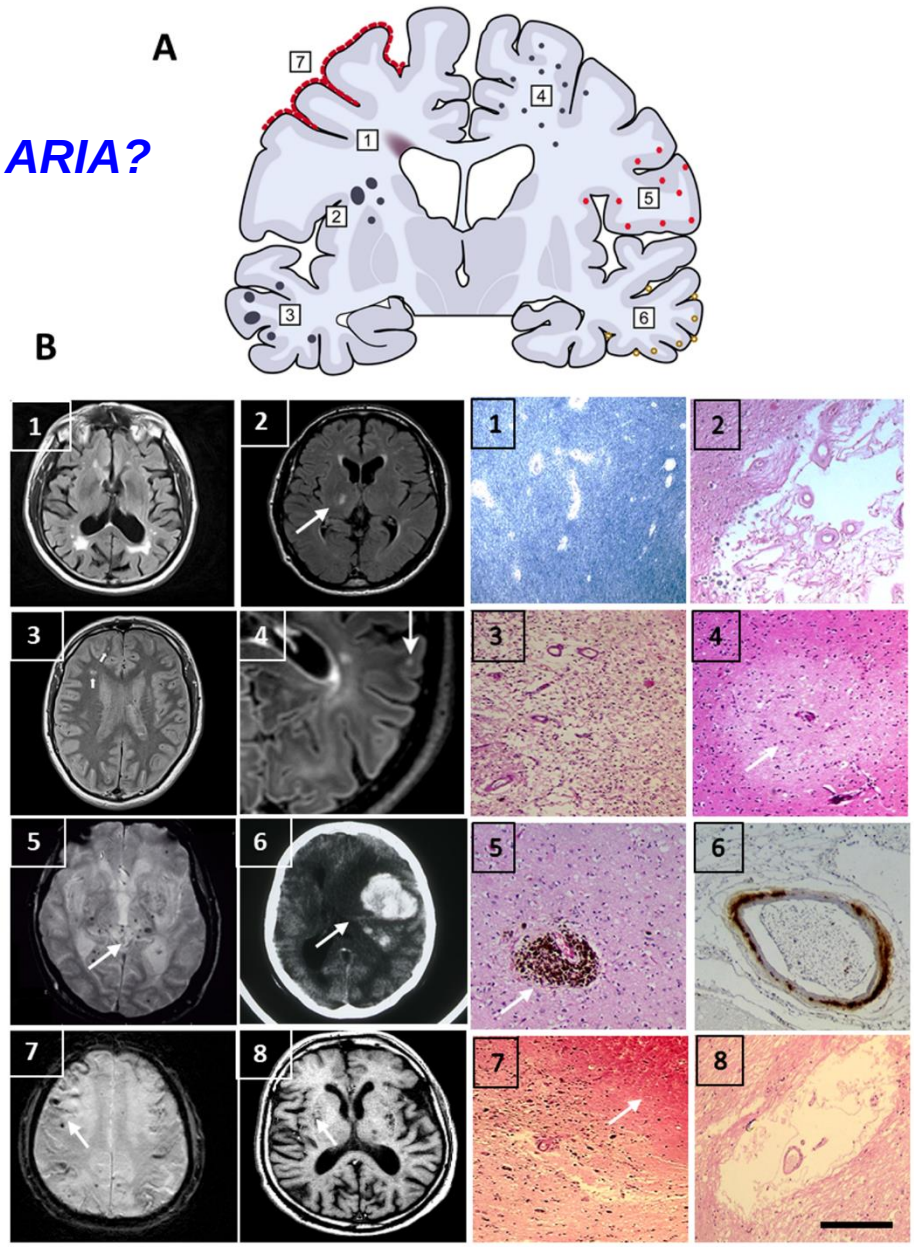
Progressive vascular and parenchymal changes linked to microangiopathies as non-amyloid e.g. hypertensive type (A) and cerebral amyloid angiopathies (B)

Key consequences:

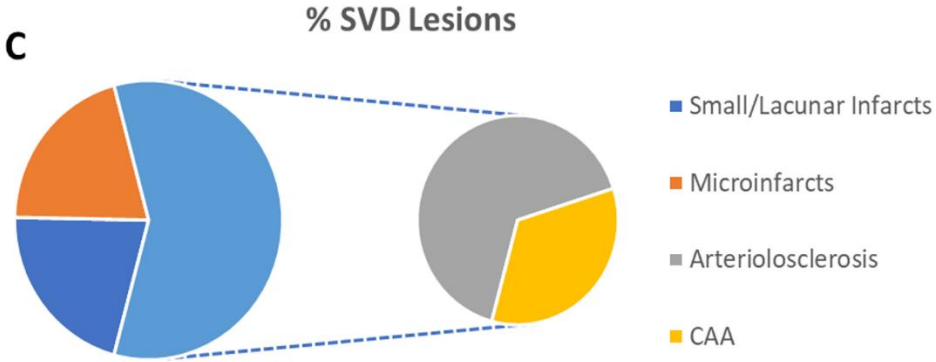
- **↑ Changes in GM (neuronal) and WM**
- **Molecular and perivascular cellular stages**
- **↑ Perivascular spacing, lacunar infarcts and *microinfarction, CMBs rare***

Arteriolosclerosis: first change in spectrum of *Vascular Lesions* in sporadic and familial AD

ARIA?

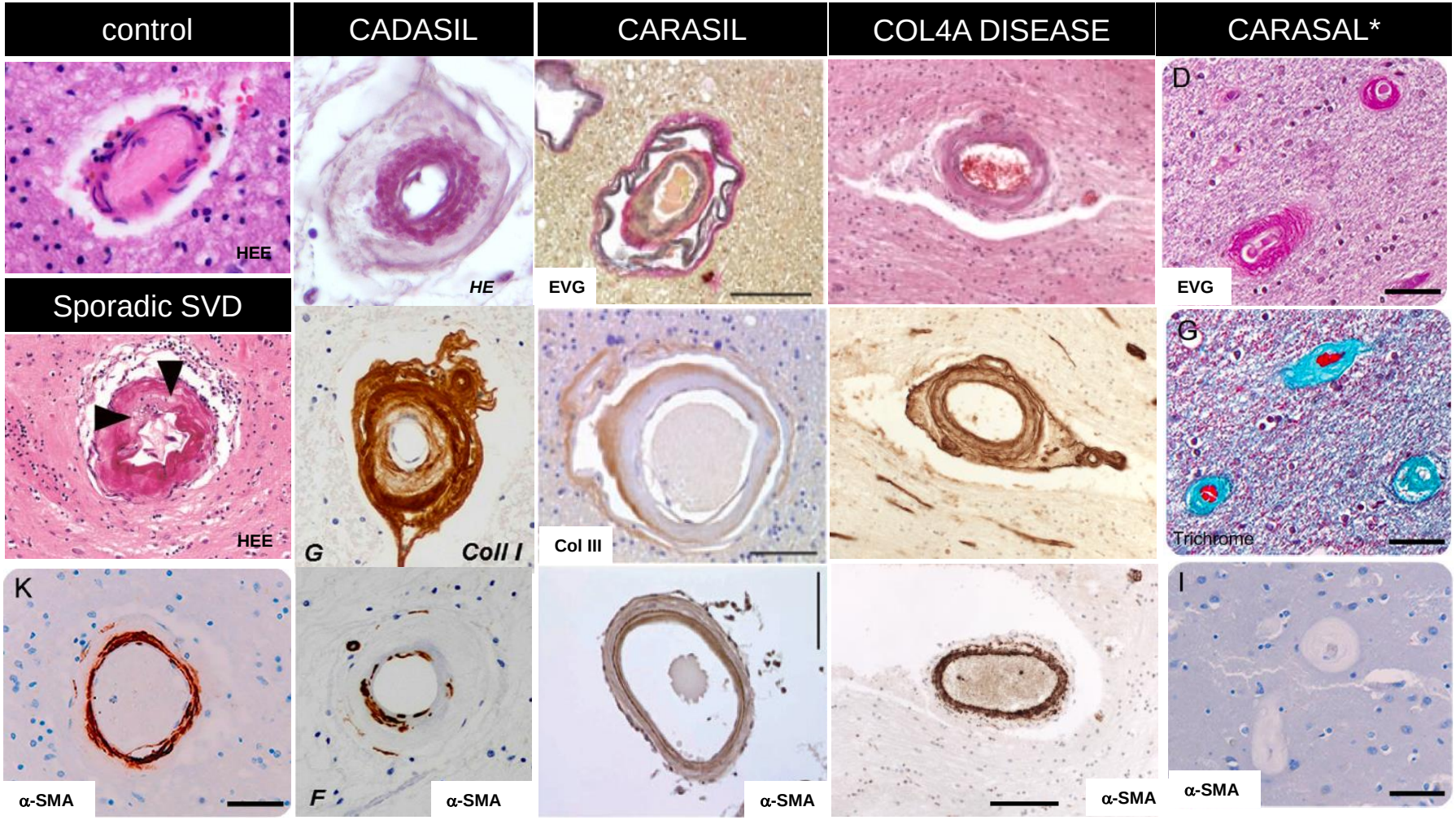


- **High proportions (>80%) of SVD pathologies:** community-based observational and longitudinal cohorts* *NACC data
- **SVD features:** ~1 lacunar infarct, microinfarct, moderate to severe arteriolosclerosis or CAA
- **BBB damage:** Increased GLUT1+ve RBCs, iron, fibrinogen, ICAM-1…



Kalaria, Sepulveda-Falla, 2021

Major disruption of Brain Microvascular ECM with loss of SMCs in sporadic and familial SVDs

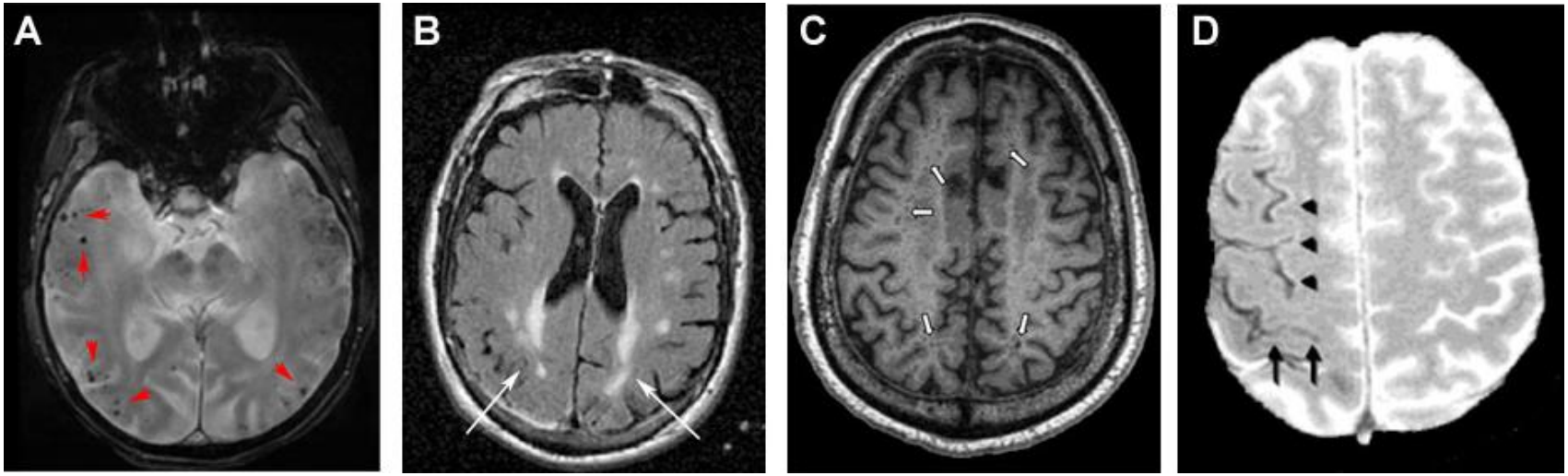


*CARASAL: hereditary adult-onset SVD.
Endothelin-1 role in pathogenesis of WMLs?

After Anne Joutel, 2017

Oide et al, 2008; Tikka et al, 2014; Bugiani et al, 2016; Charidimou et al, IJS 2015

Radiological signature of CAA



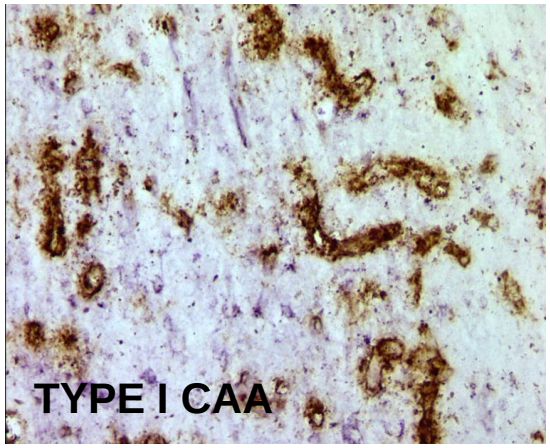
A, lobar microbleeds on GRE images; B posterior dominant WMH; C, dilated PVS on WM T1-WI; D, multiple areas of superficial siderosis

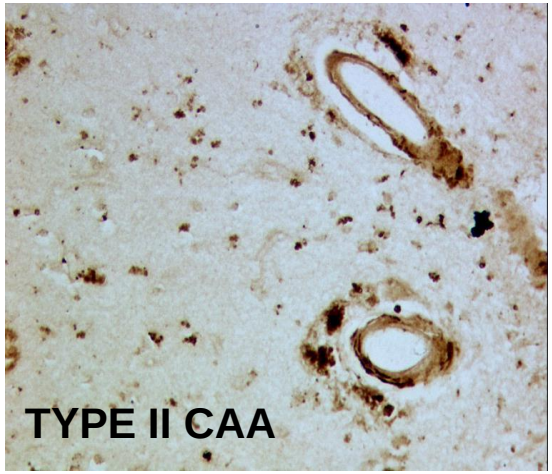
Prevalence / Incidence of CAA

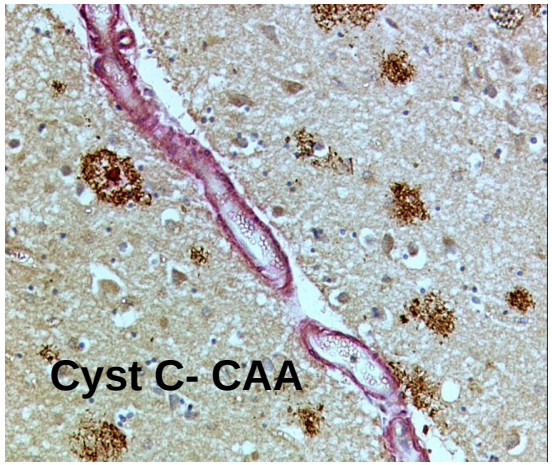
Clinicopathological studies

- Sporadic CAA ~50 % >80 yrs some pathological evidence of CAA, mostly without clinical symptoms; ~20 or more years later than hereditary CAA; cause of spontaneous ICH and cognitive impairment
- CAA is 32% in unselected community; 20-40% in non-demented and 50-60% in demented
- CAA detected in 73% - 99% of autopsy-confirmed AD
- Up to 26% with CNS biopsy specimens positive for PCNSV (granulomatous) also showed CAA
- Systemic amyloidosis (37%) and CAA (44%) shows no association in prospective population studies
- Head trauma: CAA is increased in (18-50%) in ε4 allele carriers;
- Head trauma: risk of CAA for ε4 carriers was 8.4 times vs non-carriers

Attems J et al, 2008; Salvarani C et al, 2008; Tanskanen M et al, 2006; Leclercq PD et al, 2005 Xu D et al, 2003; Tian J et al, JNNP 2004



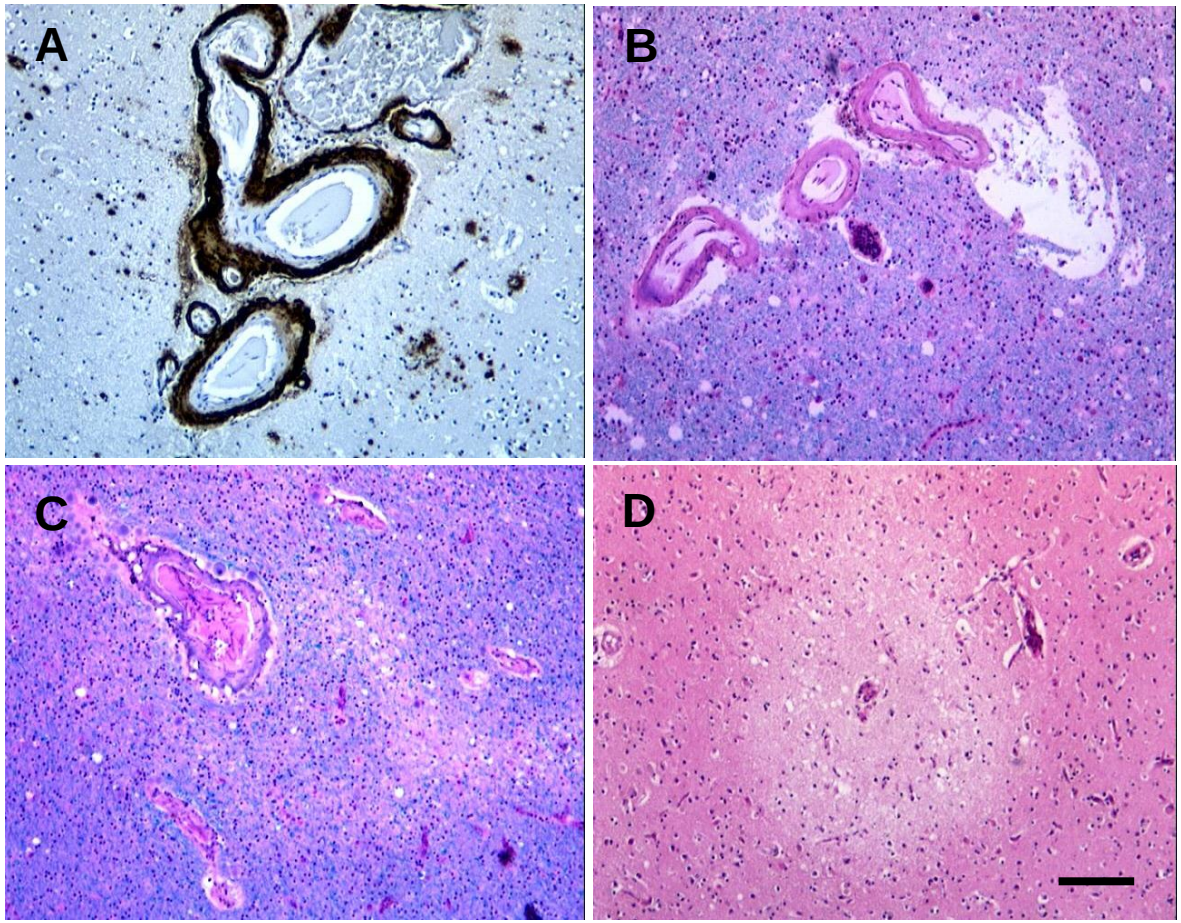




Patterns of CAA

- Increases with age, 40-50% in >80 yrs
- Most common type is Aβ CAA
- Two types: Type I capillary; Type II arteriolar CAA
- Leptomeninges, perforating arteries, cortical arterioles, perivascualr/dyshoric, rarely spinal vessels
- Occipital lobe most commonly affected; > frontal lobe; WM rarely involved
- Amyloid proteins form fibrils and may attract other proteins: ApoE, Cystatin C, protease inhibitors
- Fibrils replace in situ muscle and elastic elements to weaken vessel wall

CAA and Microvascular Pathology

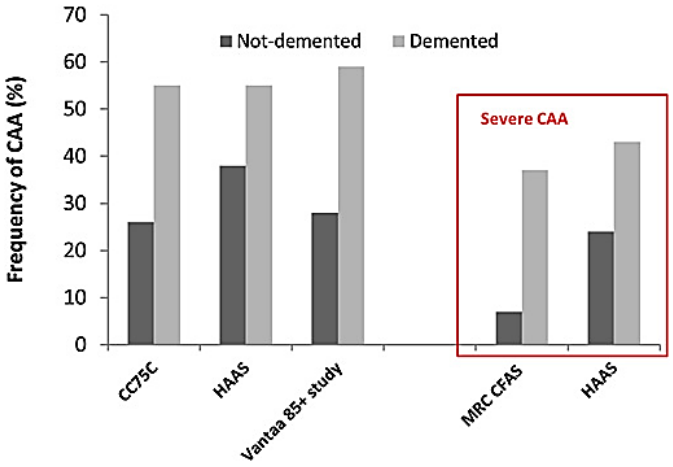


Severe CAA with loss of arterial (vascular) smooth muscle cells: substrate for chronic hypoperfusion

Microinfarcts multiply in CAA and cause focal microvascular protein deposition

Oakamoto Y et al, 2012; Kalaria R et al, 2003

Pathology of CAA and VCI/Dementia

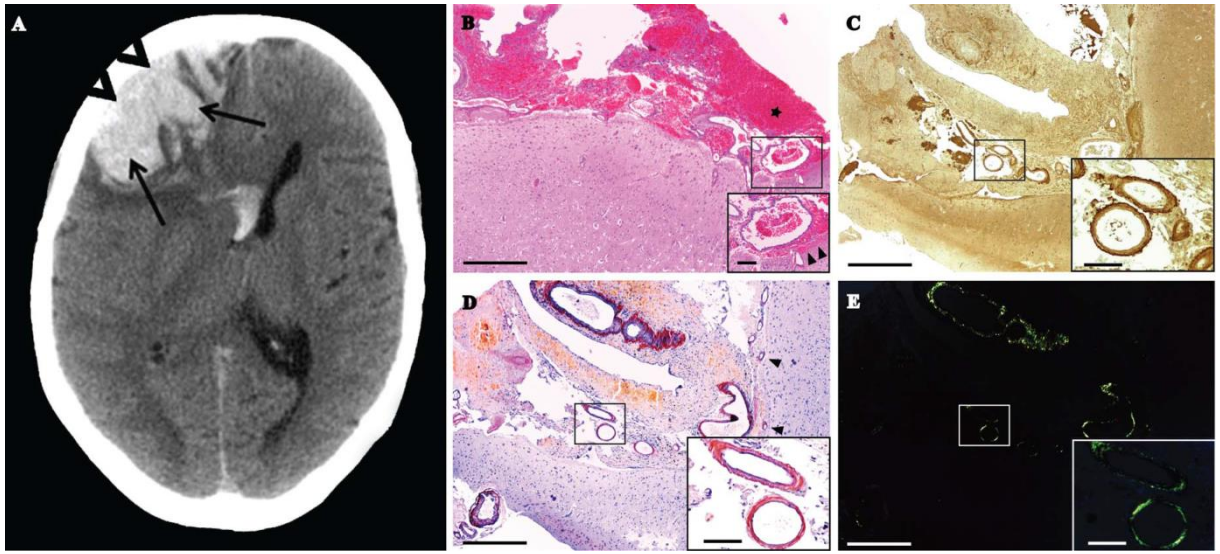


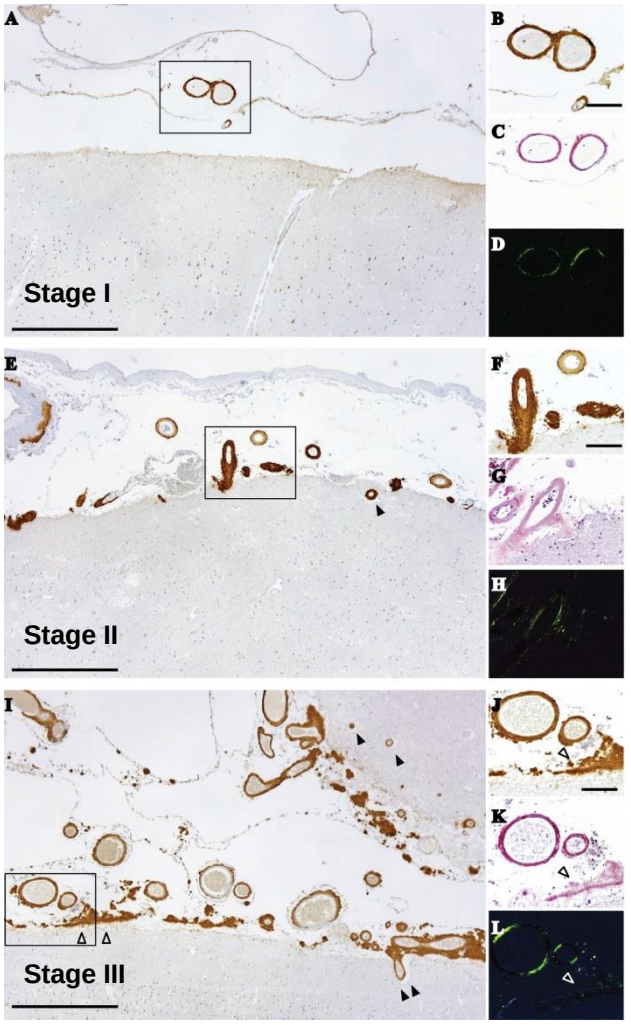
Clinicopathological evidence

- CAA is associated dementia
  - 55-59% of those with dementia displayed CAA (of any severity) vs. 28-38% of non-demented. 37-43% demented with severe CAA vs. 7-24% of non-demented
- CI and dementia in elderly sporadic CAA cases in the absence of other pathologies or factors
- CAA lowers threshold for clinical dementia
- CAA independent factor for VCI and dementia
  - HCHWA-Dutch type – ↑ CAA in demented vs non-demented; absence of SP/NFT did not explain dementia in CAA

Tanskanen M et al, 2013; Charidimou A et al, 2012; Arvanitakis Z et al, 2011; Vishwanathan A & Greenberg SM, 2011; Keage HA et al, 2009; Natte R et a, 2002; Pfeifer LA et al, 2002 ; MRCFAS, Neuropath Grp, 2001

CNS patterns of Transthyretin-related amyloidsis in Familial Amyloid polyneuropathy

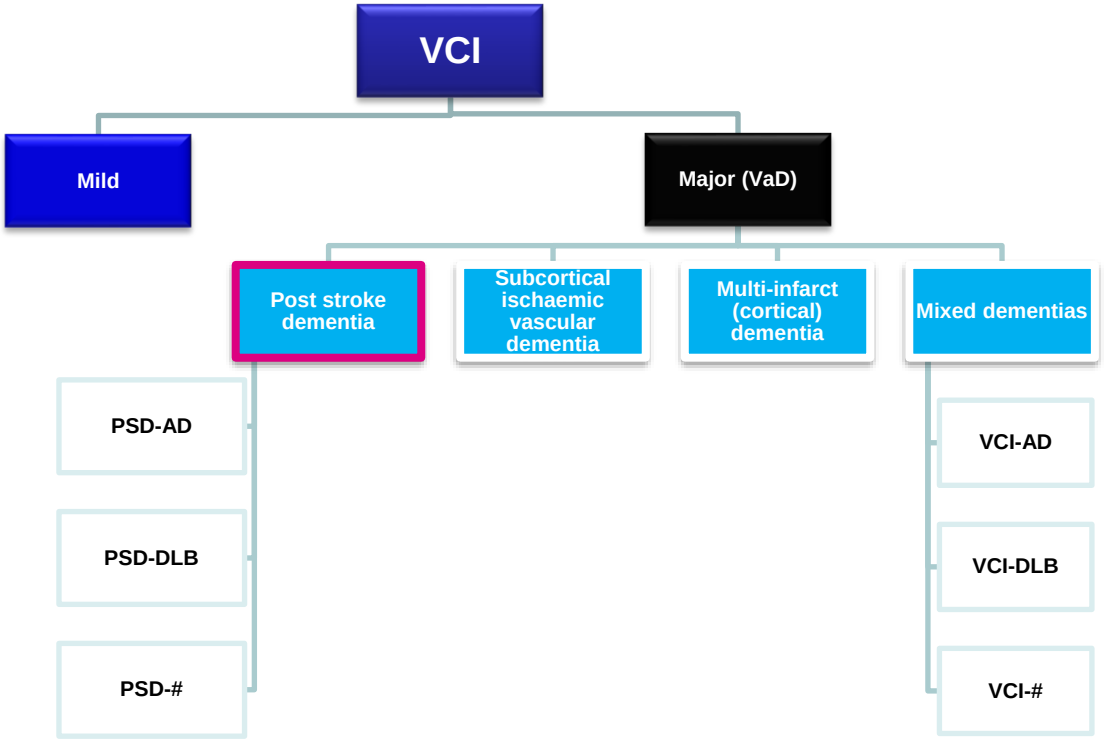




- **Onset 30-40 yrs, disease duration 6-12 yrs**
- **CNS TTR noted 3 yrs onset of peripheral neuropathy**
- **Pattern: meninges…progresses to meningocortical arteries and subpial parenchyma**
- **Subpial TTR amyloid associated with astrocytosis**
- **No cortical microbleeds, superficial siderosis or Aβ IR**

Maia LF, Magalhães R, Freitas J, et al. JNNP: doi:10.1136/ jnnp-2014-308107

Standardised Diagnosis of VCI guidelines from VICCCS Consortium



Mild VCI: Impairment in at least ONE cognitive domain and mild to no impairment in ADL (independent of motor/sensory sequelae of vascular event)

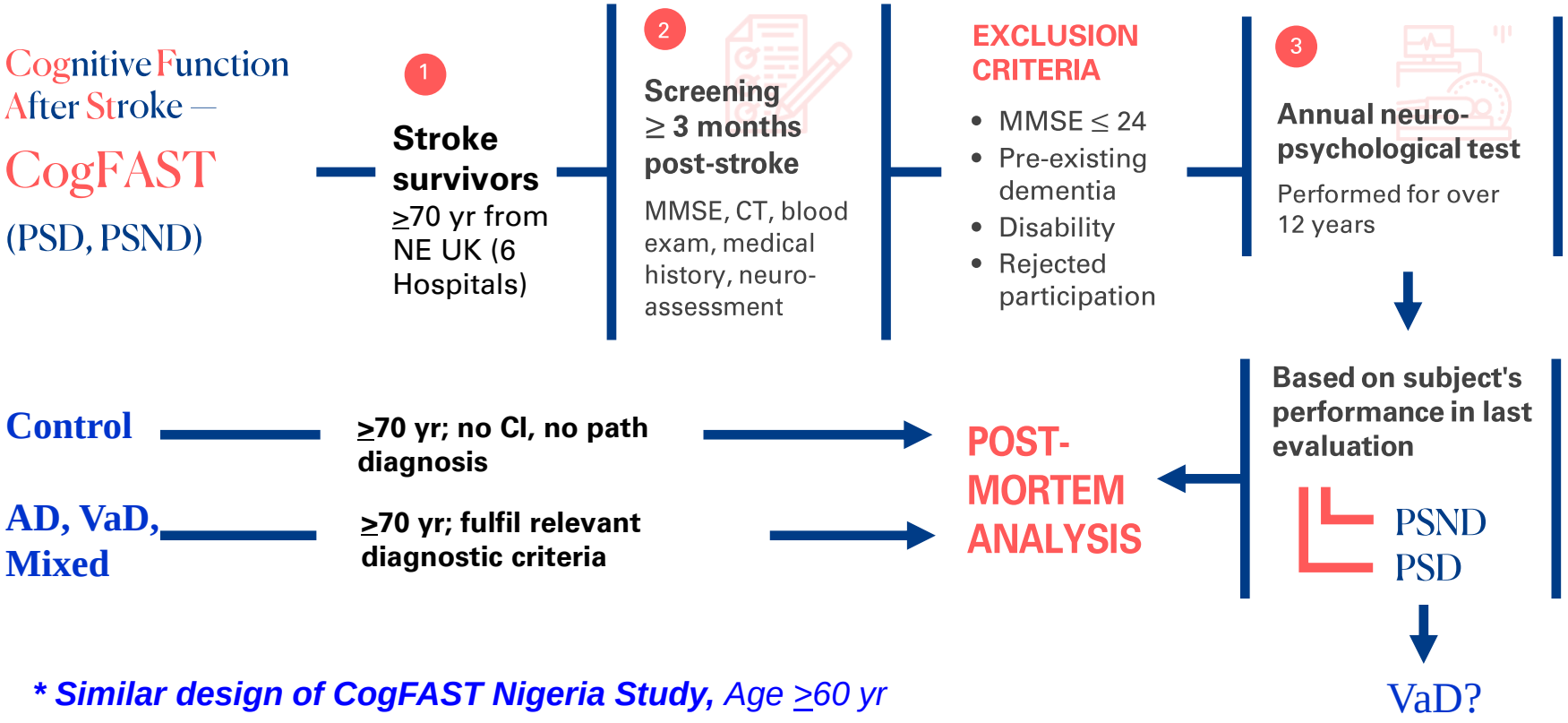
Major VCI (VaD): Clinically significant deficits of sufficient severity in *at least* ONE cognitive domain (deficits may be present in multiple domains) and severe disruption to ADL (independent of the motor/sensory sequelae of the vascular event)

- **Diagnosis of VICCCS-revised *Mild and Major forms of VCI* and endorsed the NINDS-CSN (Hachinski et al, 2006) neuropsychological assessment protocols and recommendations for imaging**
- **Core domains for assessment should include: *executive function, attention and memory as well as language and visuospatial function***

O Skrobot et al, 2017. 2018

Design of Cognitive Function After STroke (CogFAST – Newcastle Study)*

CogFAST Study Cohort

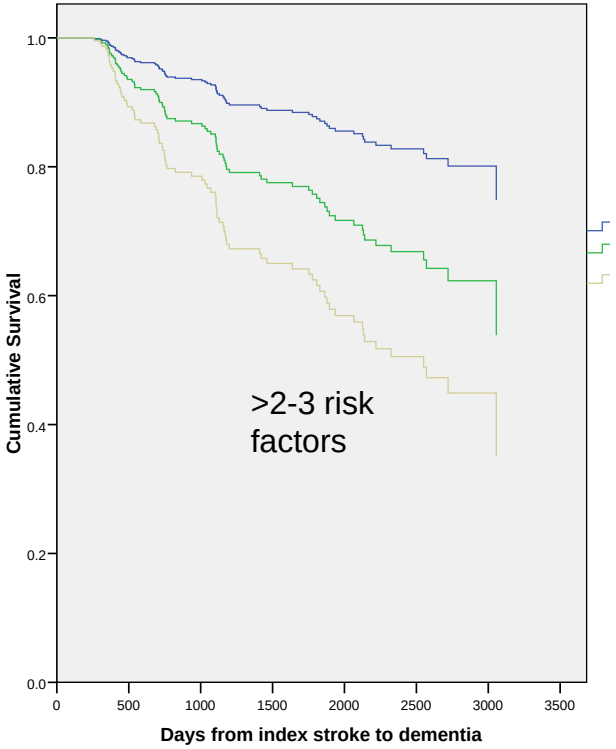


** Similar design of CogFAST Nigeria Study, Age ≥60 yr*

COGFAST study: Overall Clinical and Neuropsychometric and Neuroradiological Findings

- Elderly group
- After 5 years, ~half will have died.
- Only 1 third will be alive without VCI (Exec dysfunction) or dementia
- Greater decline to death or dementia if >2 vascular risk factors or baseline cognitive impairment but no dementia
- *Decline associated with WMLs, MTL atrophy and lower CBF*
- Incident depression 36.9 episodes per 100 person years

Time to dementia by number of cardiovascular risk factors



~20-year Longitudinal study (MRC) of post-stroke survivors: Lead PI R Kalaria

Kalaria and Ballard, 2001; Ballard C et al, Stroke, 2003; Ballard C et al, Dementia 2003 ;Ballard et al, Neurology 2004; Stephens S et al, J Am Geriatr Soc, 2003; Kalaria RN et al, 2004; Allan LM et al, 2011; Kalaria RN 2012; Allan L et al, 2013….

Trajectories of Elderly Stroke Survivors in CogFAST study

Two phases of post-stroke cognitive function prior to dementia

- *Relatively stable cognitive function for years after stroke*
- Steep decline 3 years before the dementia
- Stepwise pattern of decline – diagnostic for VaD

<u>Implications</u>: stepwise decline should alert the clinician to a possibility of impending VaD; support strict control of vascular risk factors in stroke survivors

Delgado J, Hase Y, Akinyemi R, Kalaria R, Allan L (2022); Kalaria R et al, in preparation

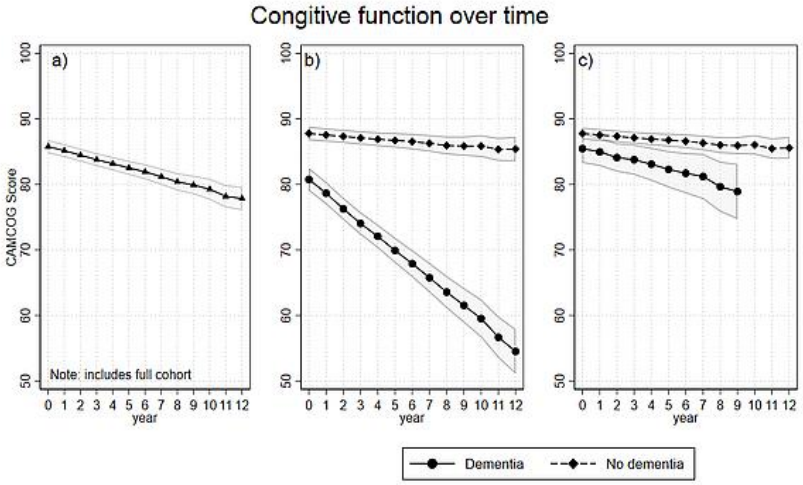


Table 1: CogFast participant characteristics

COGFAST Cohort (N=355)	Dementia	No dementia	p value
Number	91	264	
Female (%)	57.1%	45.1%	0.05
Age at baseline	80.3 (4.5)	80.1(4)	0.66
Cognitive measures			
CAMCOG-R (baseline)	80.6 (9.3)	86.6 (8.3)	<0.01
CAMCOG-R (end of follow-up)	59.2 (16.8)	86.7 (9.8)	<0.01
Change in CAMCOG-R	-21.6 (17.7)	-1.2 (9.6)	<0.01
MMSE (baseline)	24.7 (3.1)	26.6 (2.5)	<0.01
MMSE (end of follow-up)	20.1 (3.9)	25.8 (3.5)	<0.01
Change in MMSE	-4.6 (4.3)	-0.8 (3.1)	<0.01
Full scale IQ	105.9 (12.3)	108.2 (10.8)	0.12

1) Kalaria et al, BBA - Mol Basis Dis. 2016; Mijajlović et al. BMC Med. 2017; Bigler et al. TBI Res 2015

COGFAST study: SVD, Vascular Risk Factors and Pathological Diagnosis of VaD

doi:10.1093/brain/awr273 Brain 2011: 134; 3713–3724 | 3713

BRAIN
A JOURNAL OF NEUROLOGY

Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors

Louise M. Allan, Elise N. Rowan, Michael J. Firbank, Alan J. Thomas, Stephen W. Parry, Tuomo M. Polvikoski, John T. O'Brien and Raj N. Kalaria

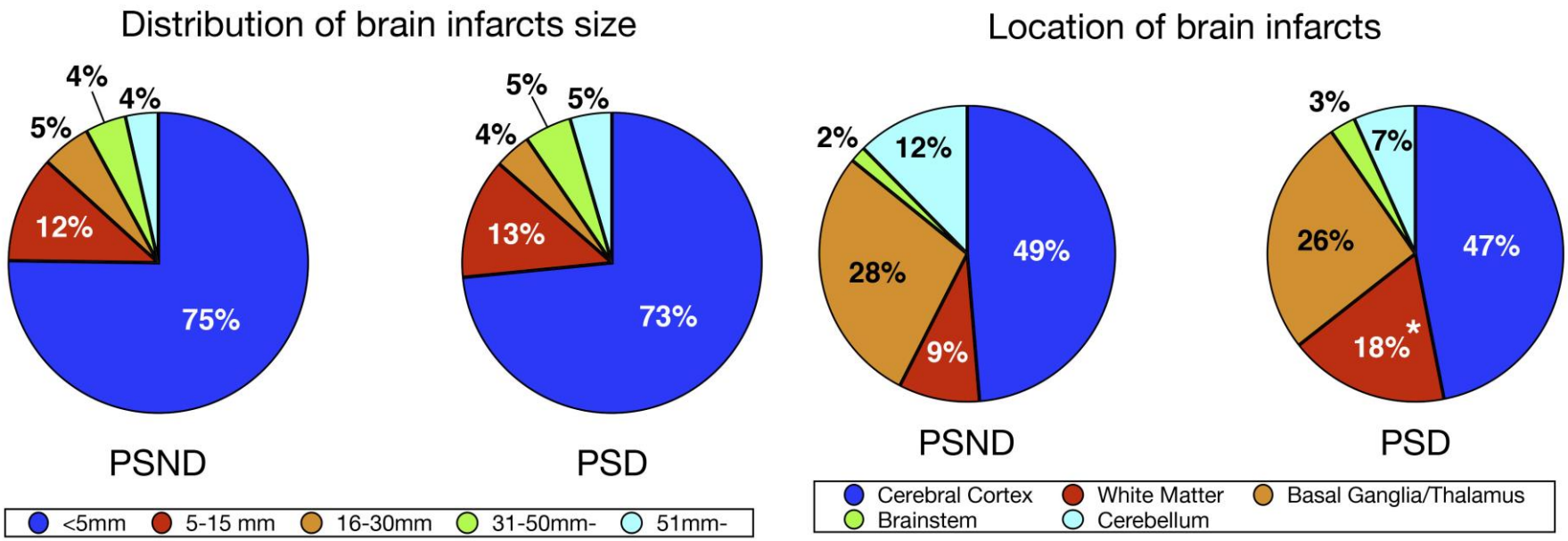
Institute for Ageing and Health, Newcastle University, Wolfson Research Centre, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK

Correspondence to: Prof. Raj N. Kalaria

- During mean follow-up of 3.8 years, ~25% developed PSD
- Neuropsychological features: Executive dysfunction, memory deficits
- Medial Temporal Lobe (MTL) atrophy over the years
- Survival (days from baseline stroke to death) and overall burden of vascular pathology (Braak <2.5; CERAD 0-1) similar between PSD and PSND
- Majority stroke survivors develop VaD: Pathological diagnosis indicated ~78% VaD, rest Mixed (AD type pathology with vascular lesions) and frontotemporal dementia (1)
- Microinfarction/small lesions differentiate PSD from dementia free PS survivors

Ballard C et al, 2003; Kalaria RN et al, 2004; Firbank M et al, 2007, 2011, 2012; Allan L et al, 2012; 2013, Deramecourt V et al, 2012; Kalaria et al in preparation

COGFAST study: PSND versus PSD relative to Cerebral Infarct Size and Location



**Location of Infarcts in WM (red) separated PSD (decliners) from PSND (stable)*

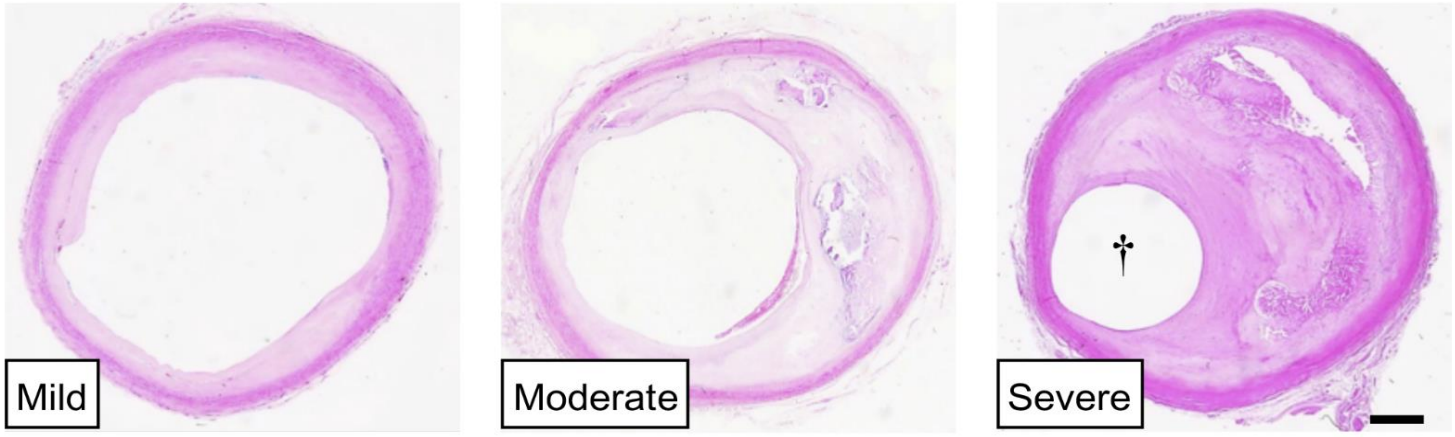
Most infarcts <5 mm; cortical Infarcts and lacunes

PSND = post-stroke non-demented
PSD = post-stroke demented

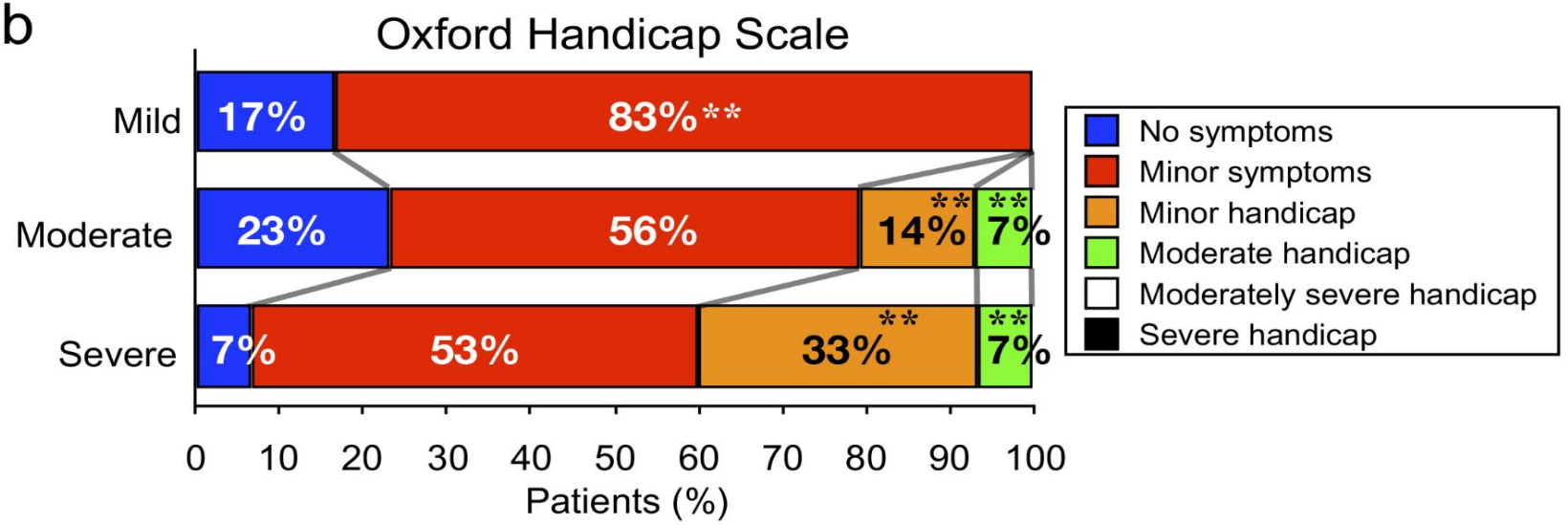
Hase Y et al, 2019

COGFAST study: Severity of Carotid Artery Disease (CAD) and Function (ADL)

a



b



↑ % ADLs (minor handicap or moderate symptoms) consistent with moderate- severe ICA stenosis

Hase Y et al, 2019

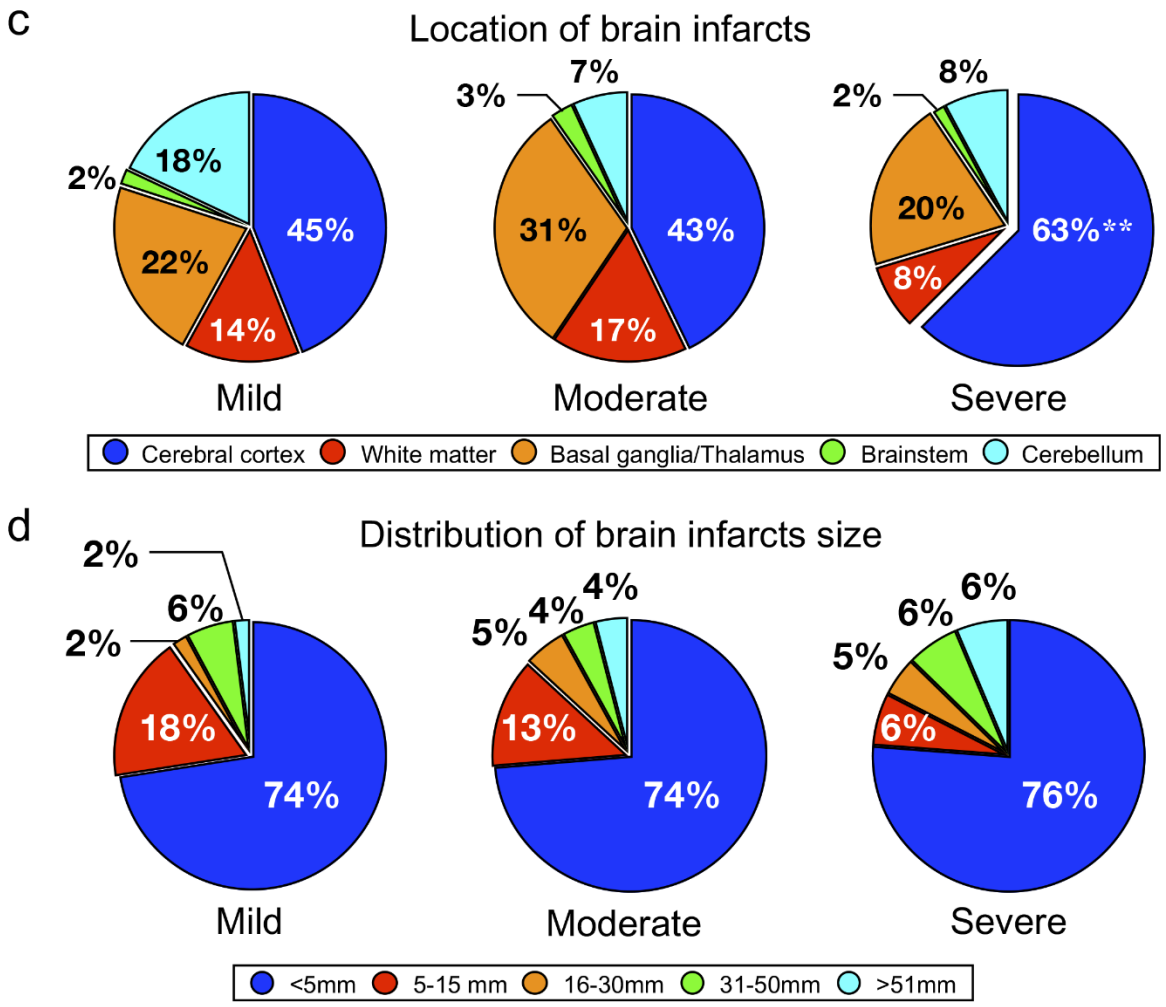
COGFAST study: Severity of Carotid Artery Disease (CAD), Dementia and VRFs

bar=1mm

Dementia (%)	**16.7%****	**60.5%**	**66.7%**
Hypertension (%)	**50.0%**	**58.1%**	**73.3%**
Hyperlipidemia (%)	**0.0%**	**9.3%**	**40.0%****
IHD (%)	**8.0%**	**30.0%**	**67.0%****
smoking/AF/DM (%)	**50/8/0 %**	**61/14/5 %**	**67/20/13 %**

Hase Y et al, 2019

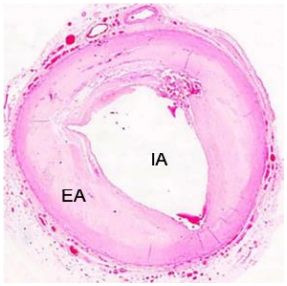
COGFAST study: Severity of CAD associated with greater numbers of *small cortical infarcts*

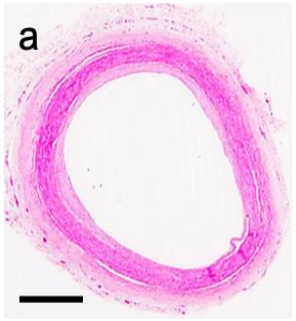


Hase Y et al, 2019

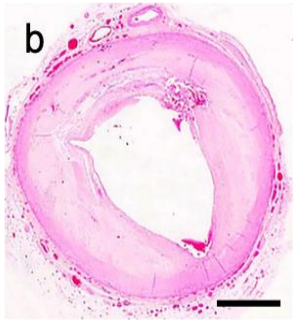
COGFAST study: Coronary Artery Stenosis and Cardiac Pathology

$$\frac{\text{External Area} - \text{Internal Area}}{\text{External Area}} \times 100$$

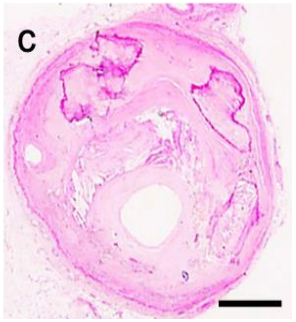




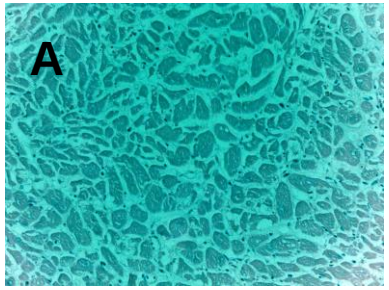
< 70 %

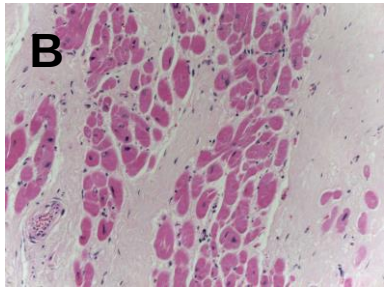


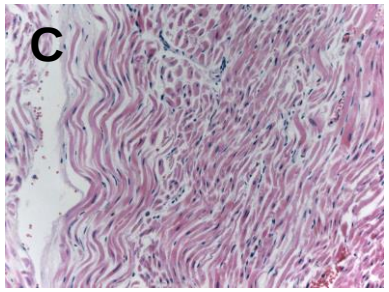
70% - 90%



> 90 %





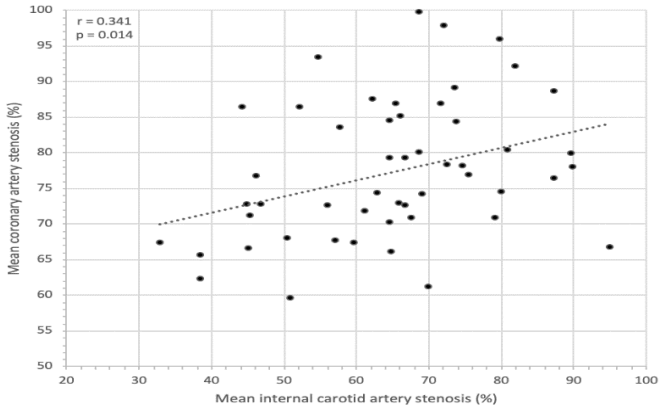


Coronary artery stenosis severity consistent with greater degree of cardiac pathology

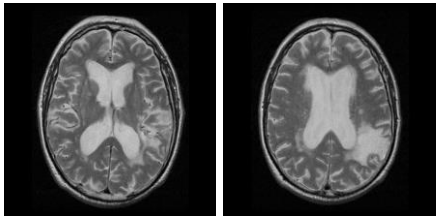
A, Necrosis; B, Fibrosis, C, Disarray

COGFAST study: Contribution of Coronary Artery Pathology to Cerebral Vascular Pathology (SVD)

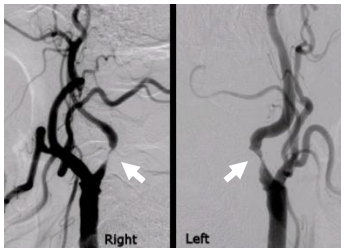
- *Significant relationship between coronary artery and ICA stenosis*
- No apparent relationship between total cerebral infarcts and % coronary artery stenosis
- Coronary artery stenosis did not differentiate PSND and PSD subjects



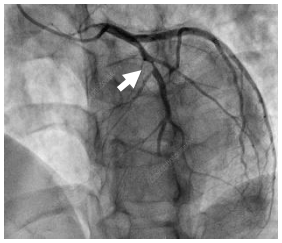
PSND = post-stroke non-demented
PSD = post-stroke demented



Cerebral Infarction



ICA stenosis



R & L Cor A stenosis

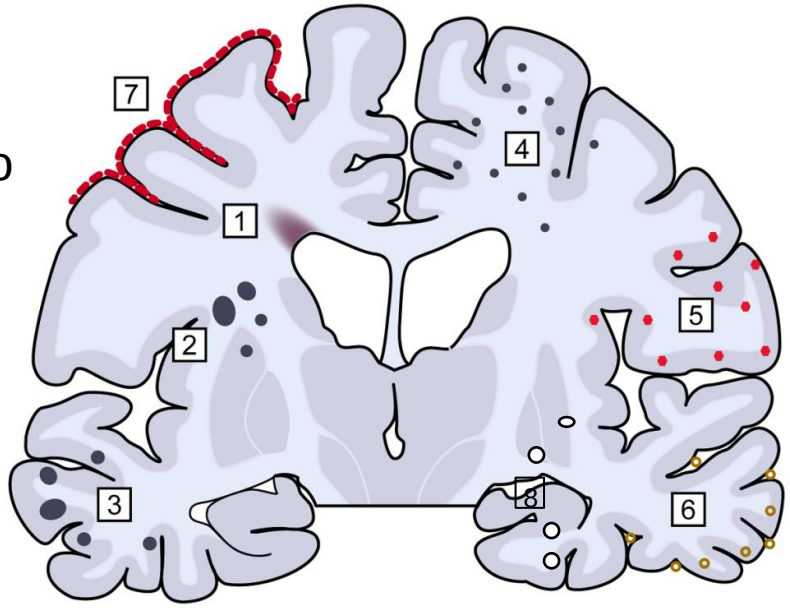
Key Point: Not all SVD pathology is of intracranial origin

Hase Y Kalaria R, et al, 2022, in preparation

SVD: Pathologists see much more than the Radiologists!

Neuroimaging (MR)

1. Periventricular and Deep WMH
2. Lacunes and macro infarcts
3. Cortical: small infarcts
4. Subcortical: macroinfarcts
5. Cerebral Microbleeds
6. Amyloid deposition (PET)
7. Superficial siderosis
8. Perivascular spaces



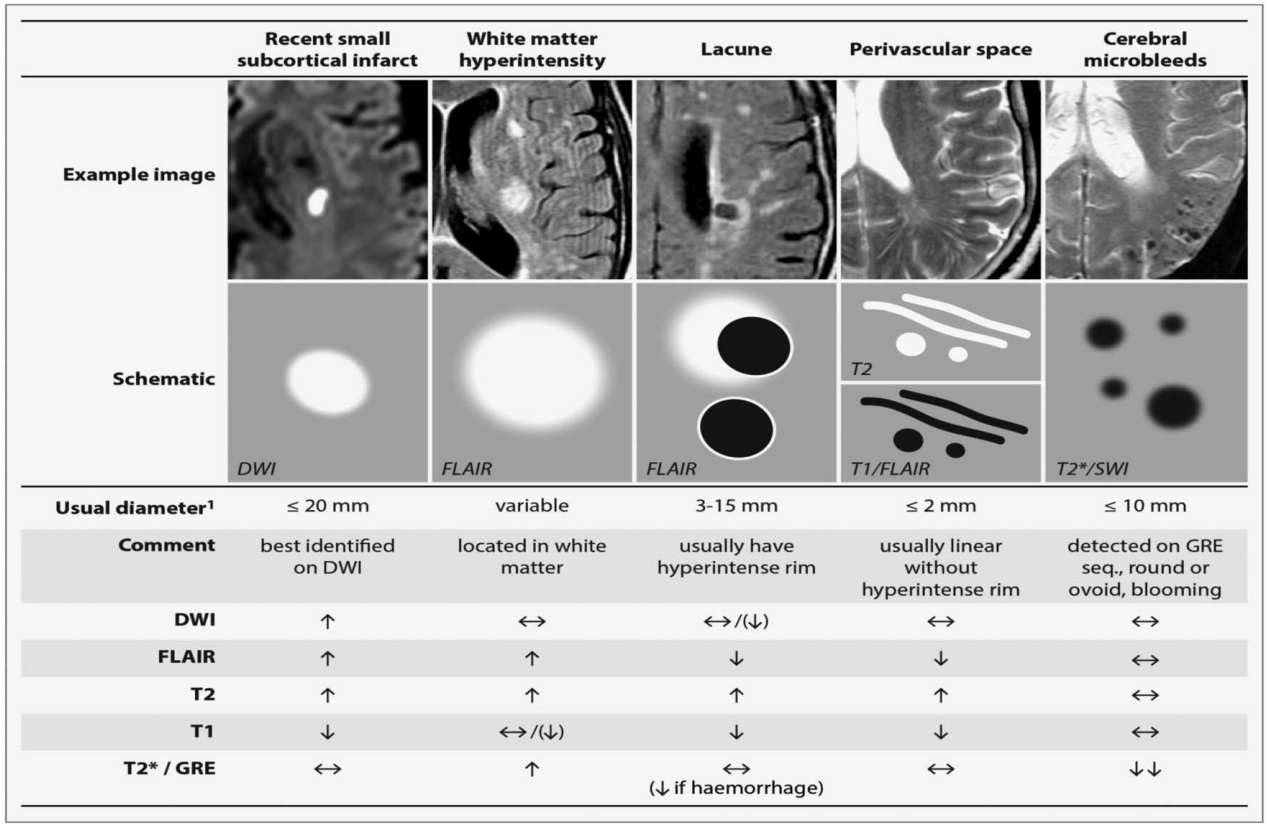
Neuropathology

1. Periventricular and DWM changes (myelin loss)
2. Subcortical infarcts: Lacunes and macro infarcts
3. Cortical: small infarcts
4. Cortical and Subcortical microinfarcts
5. Microhaemorrhages/ haemosiderin
6. Cerebral Amyloid Angiopathy
7. Superficial haemosiderin (some)
8. Perivascular spaces

Arteriolosclerosis!

Kalaria R et al, 2013

Cerebral Small Vessel Disease: Radiological Definition



	Recent small subcortical infarct	White matter hyperintensity	Lacune	Perivascular space	Cerebral microbleeds
Example image					
Schematic	DWI	FLAIR	FLAIR	T2 / T1/FLAIR	T2*/SWI
Usual diameter[1]	≤ 20 mm	variable	3-15 mm	≤ 2 mm	≤ 10 mm
Comment	best identified on DWI	located in white matter	usually have hyperintense rim	usually linear without hyperintense rim	detected on GRE seq., round or ovoid, blooming
DWI	↑	↔	↔/(↓)	↔	↔
FLAIR	↑	↑	↓	↓	↔
T2	↑	↑	↑	↑	↔
T1	↓	↔/(↓)	↓	↓	↔
T2* / GRE	↔	↑	↔ (↓ if haemorrhage)	↔	↓↓

- WMH frequencies 11-21% in 64 year-olds
- Increase to 94% by age 82 with slightly higher in women
- WMH are more common and extensive in patients with VRFs, increase risk of stroke, dementia and death.
- Heritability of WMH is as high as 45-73%.

STRIVE, STandards for Reporting and Imaging of SVD: example findings (upper), schematic representation (middle) and summary of imaging characteristics (lower) of MRI features in SVD

Wardlaw J et al, TLN, 2013

And Finally….

The learning objectives

Conclusions: VCI and Neuropathology

- Definitions, Sampling, CVD pathology spectrum
- Rare causes of VCI - vasculitis, aneurysms
- Multiple substrates involved in VCI
- Vessel changes: arteriolosclerosis and CAA are important
- SVD Pathology (VSMC degeneration/ fibroid necrosis, hyalinosis) leading small infarcts, microinfarction; PVS**,** data not clear
- White matter degeneration- myelin loss, axonal abnormalities, clasmatodendrosis, pericytes, BBB damage
- Mechanisms and consequences

VasCog 2023

Gothenburg, Sweden 13-16 September 2023

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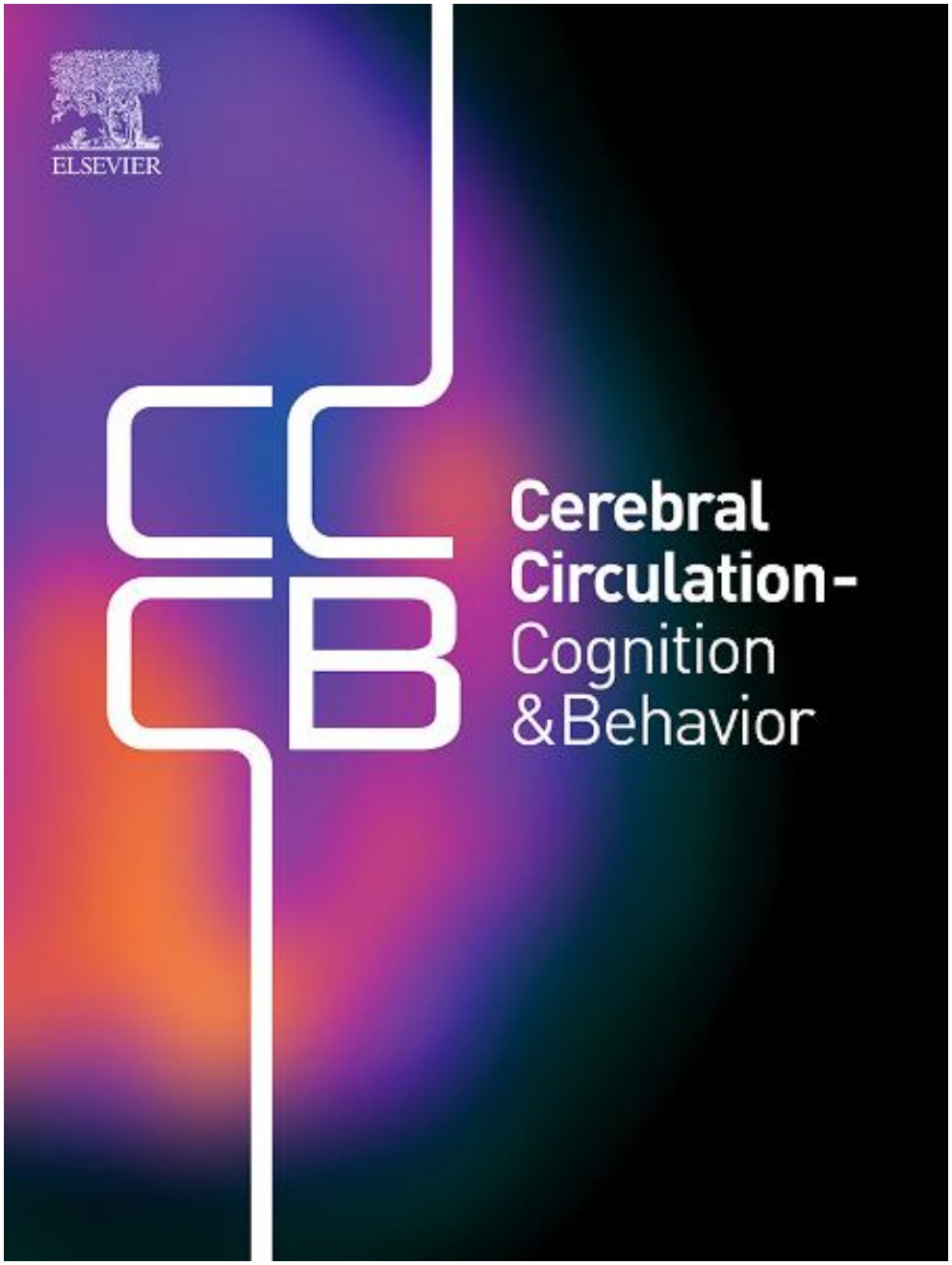
The Congress of the International Society of Vascular Behavioural and Cognitive Disorders

Abstract submission from March 1 to June 7, 2023

Early bird registration from March 1 to June 14, 2023



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