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STRIVE – Neuroimaging Standards for Measuring and Reporting Vascular Changes in Neurodegeneration

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CCD, October 5

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STRIVE standards| Funding

- Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE)
- Medical Research Council (MRC)
- Canadian Institutes of Health Research (CIHR)
- Canadian Stroke Network

- Dr Smith reports funding from CIHR, CSN, HSFC, Alz Society

Workshop| Funding

- Unrestricted grant from GE Healthcare

Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration

Joanna M Wardlaw, Eric E Smith, Geert J Biessels, Charlotte Cordonnier, Franz Fazekas, Richard Frayne, Richard I Lindley, John T O'Brien, Frederik Barkhof, Oscar R Benavente, Sandra E Black, Carol Brayne, Monique Breteler, Hugues Chabriat, Charles DeCarli, Frank-Erik de Leeuw, Fergus Doubal, Marco Duering, Nick C Fox, Steven Greenberg, Vladimir Hachinski, Ingo Kilimann, Vincent Mok, Robert van Oostenbrugge, Leonardo Pantoni, Oliver Speck, Blossom C M Stephan, Stefan Teipel, Anand Viswanathan, David Werring, Christopher Chen, Colin Smith, Mark van Buchem, Bo Norrving, Philip B Gorelick, Martin Dichgans; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1)

Lancet Neurol 2013; 12: 822–38

Cerebral small vessel disease (SVD) is a common accompaniment of ageing. Features seen on neuroimaging include

STRIVE = STandards for ReportIng Vascular changes on nEuroimaging

Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822-838

Email: eesmith@ucalgary.ca.

Outline

- Importance of Small Vessel Disease
- STRIVE Methods
- Consensus Recommendations for Terminology and Definitions of Small Vessel Disease
- Case Examples

Cerebral Small Vessel Disease

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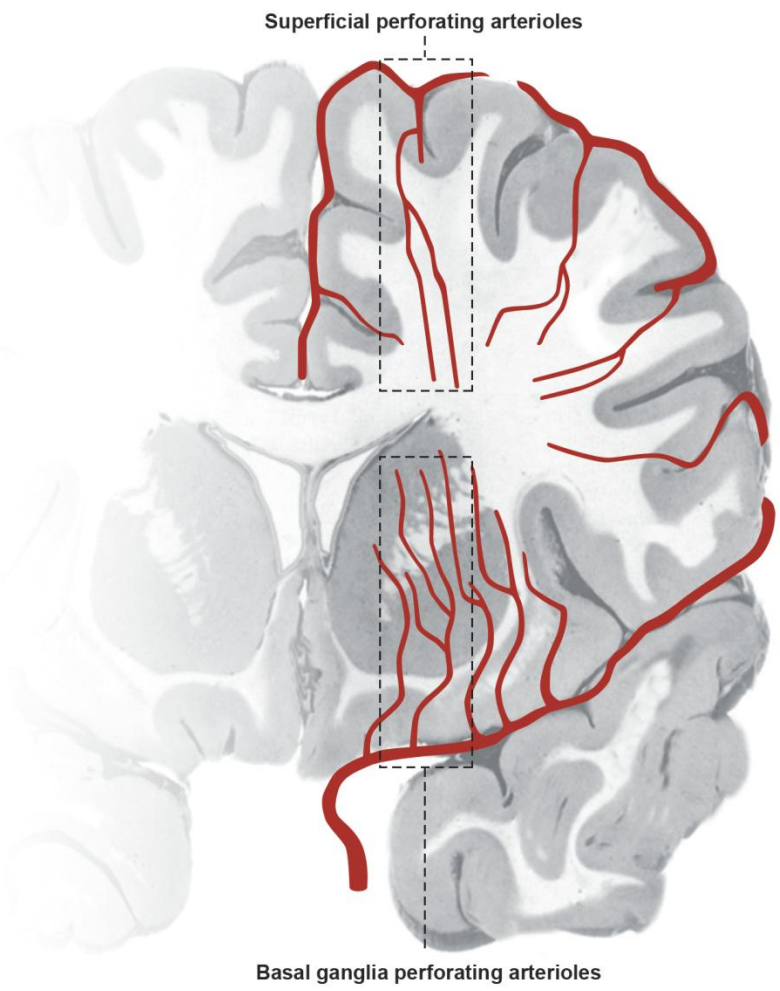

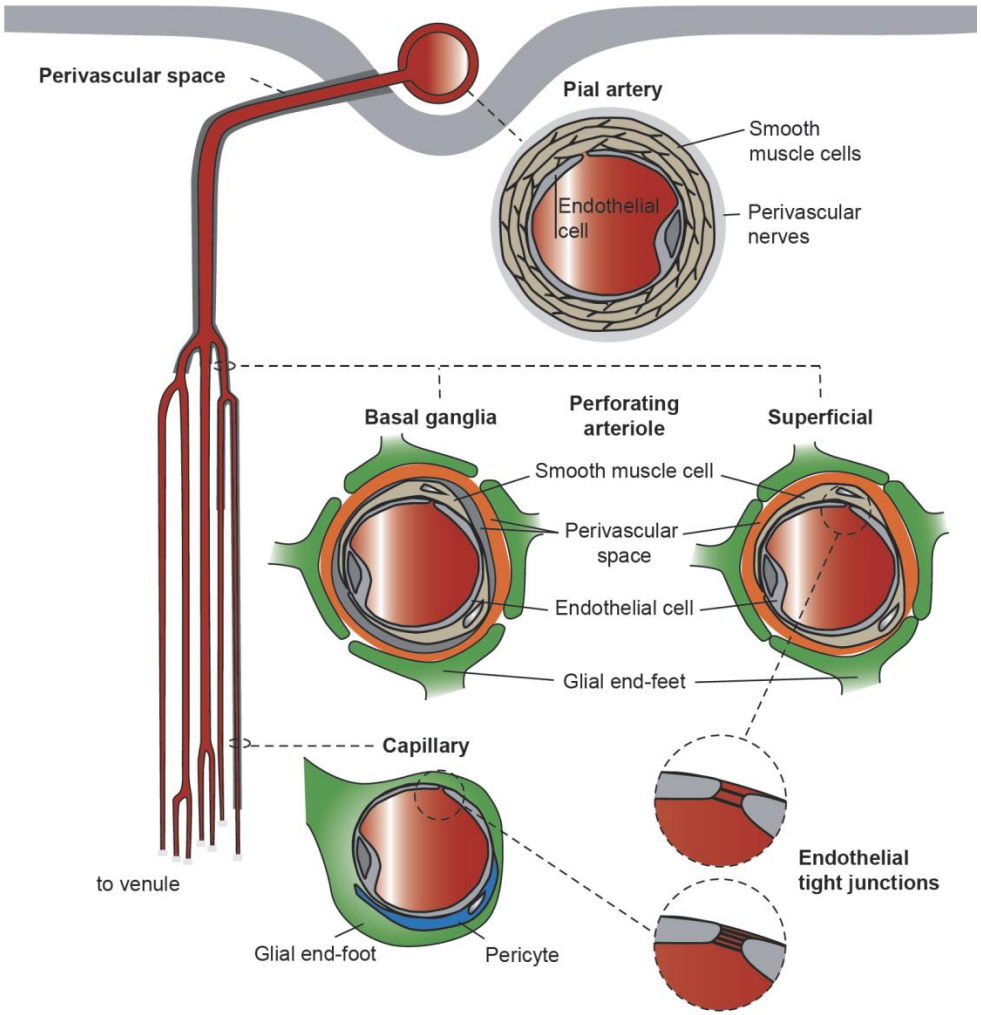

Cerebral Small Vessel Disease is common

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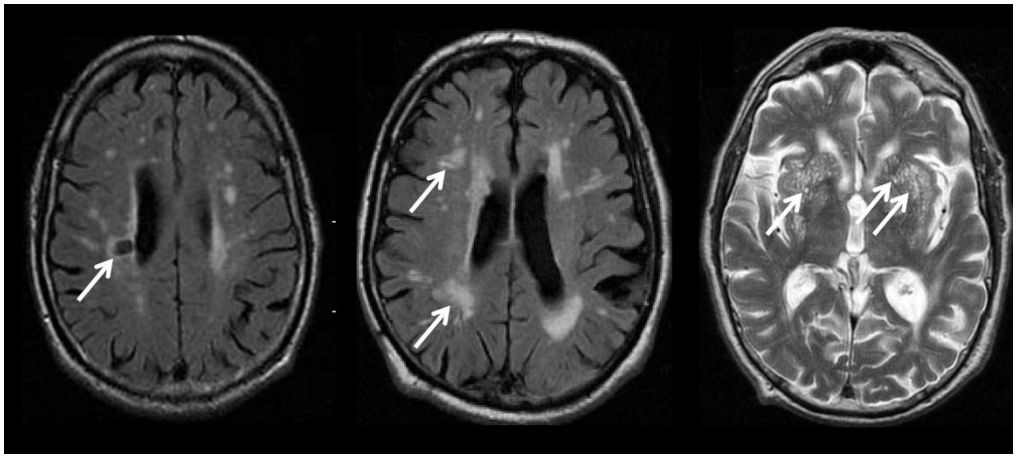
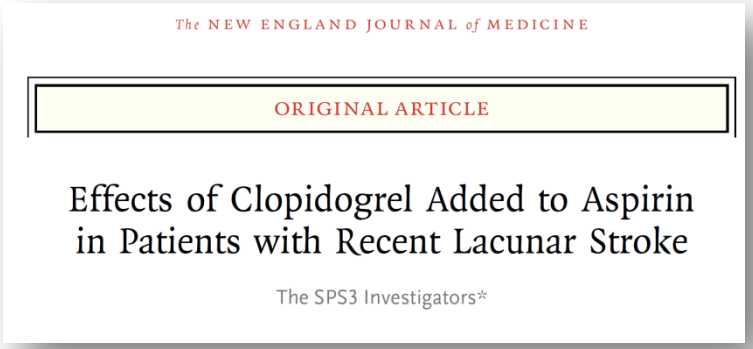
Common cause of

- **lacunar stroke**
- **ICH**
- **cognitive impairment**
- behavioral deficits
- gait disturbance
- other





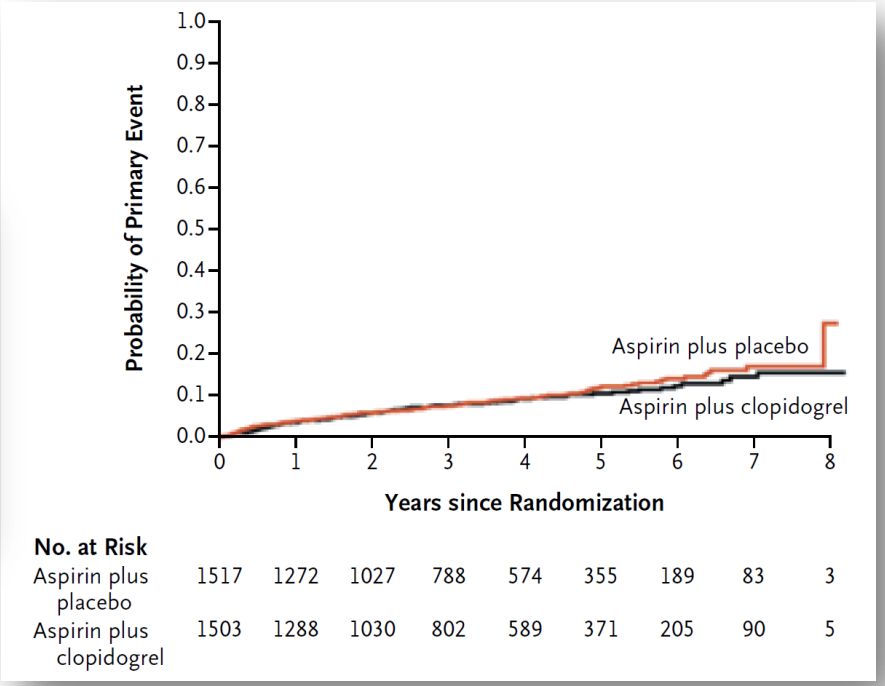
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke

The SPS3 Investigators*

Benavenet et al New Engl J Med 2012



Multiple Manifestations of SVD on Neuroimaging

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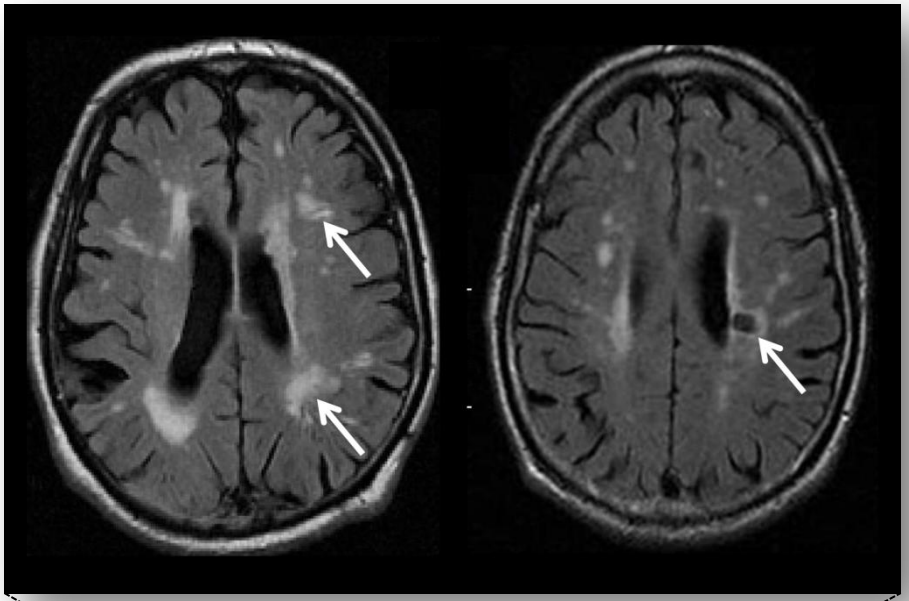
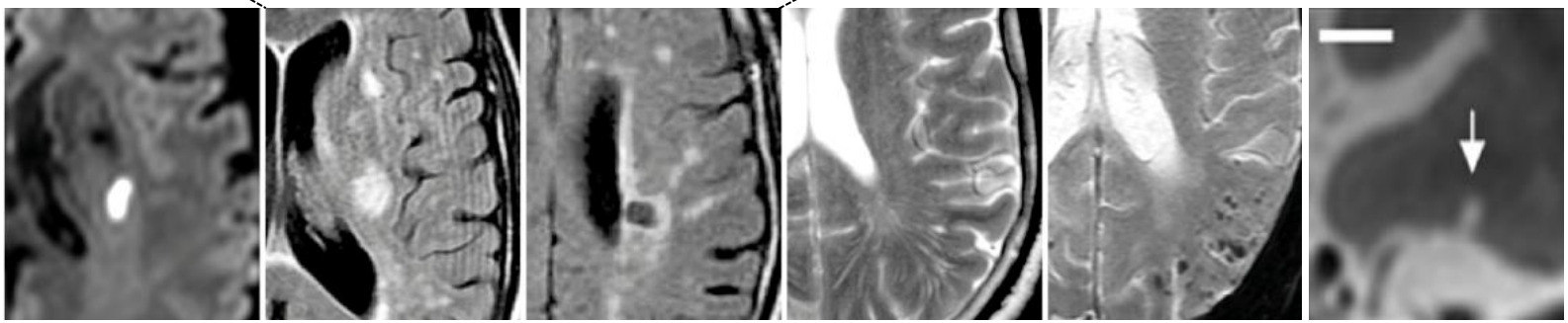


recent WMH lacunes PVS microbleed microinfarct



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Variable Fate of Lesions

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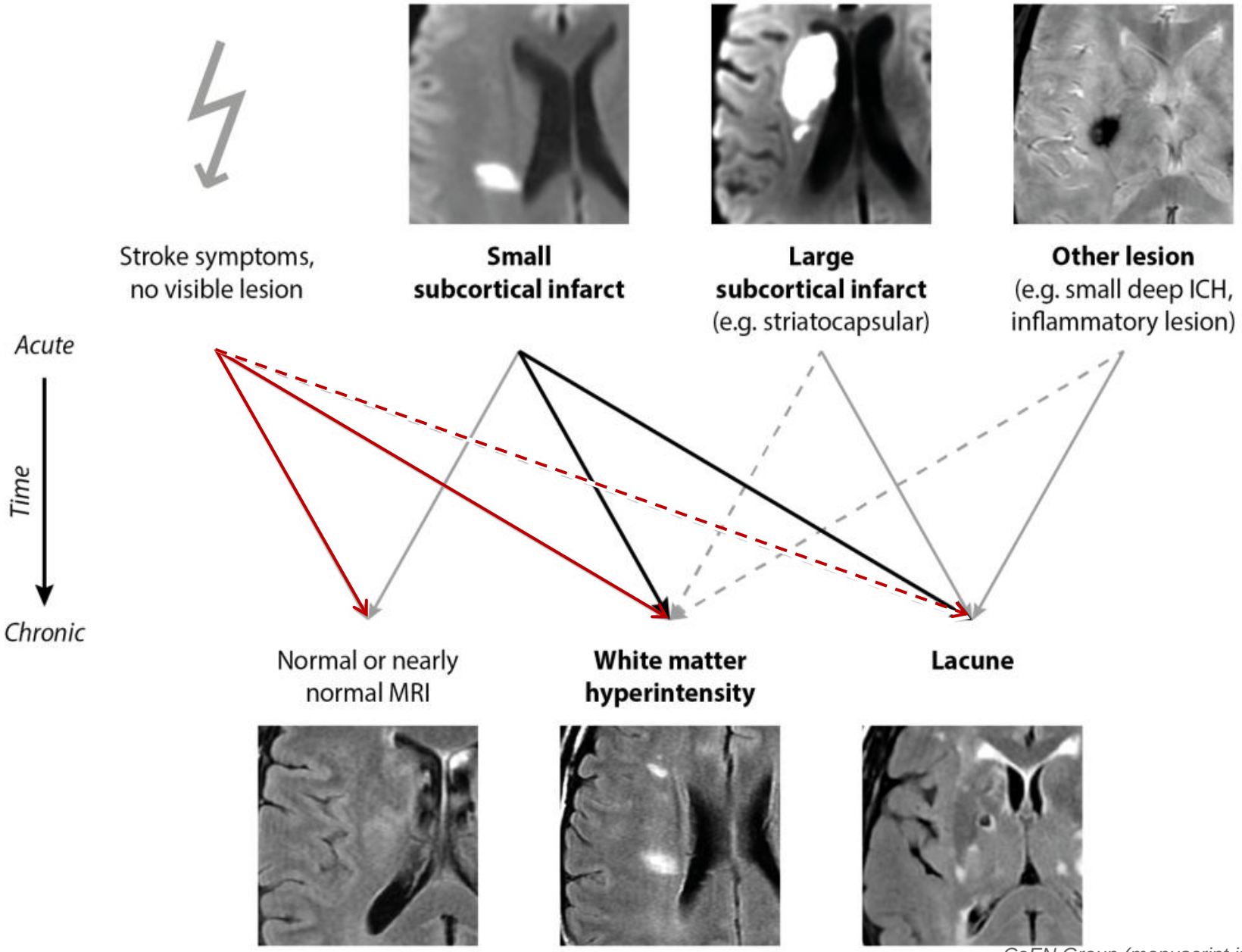

CoEN Group (manuscript in preparation)

Variable Fate of Lesions

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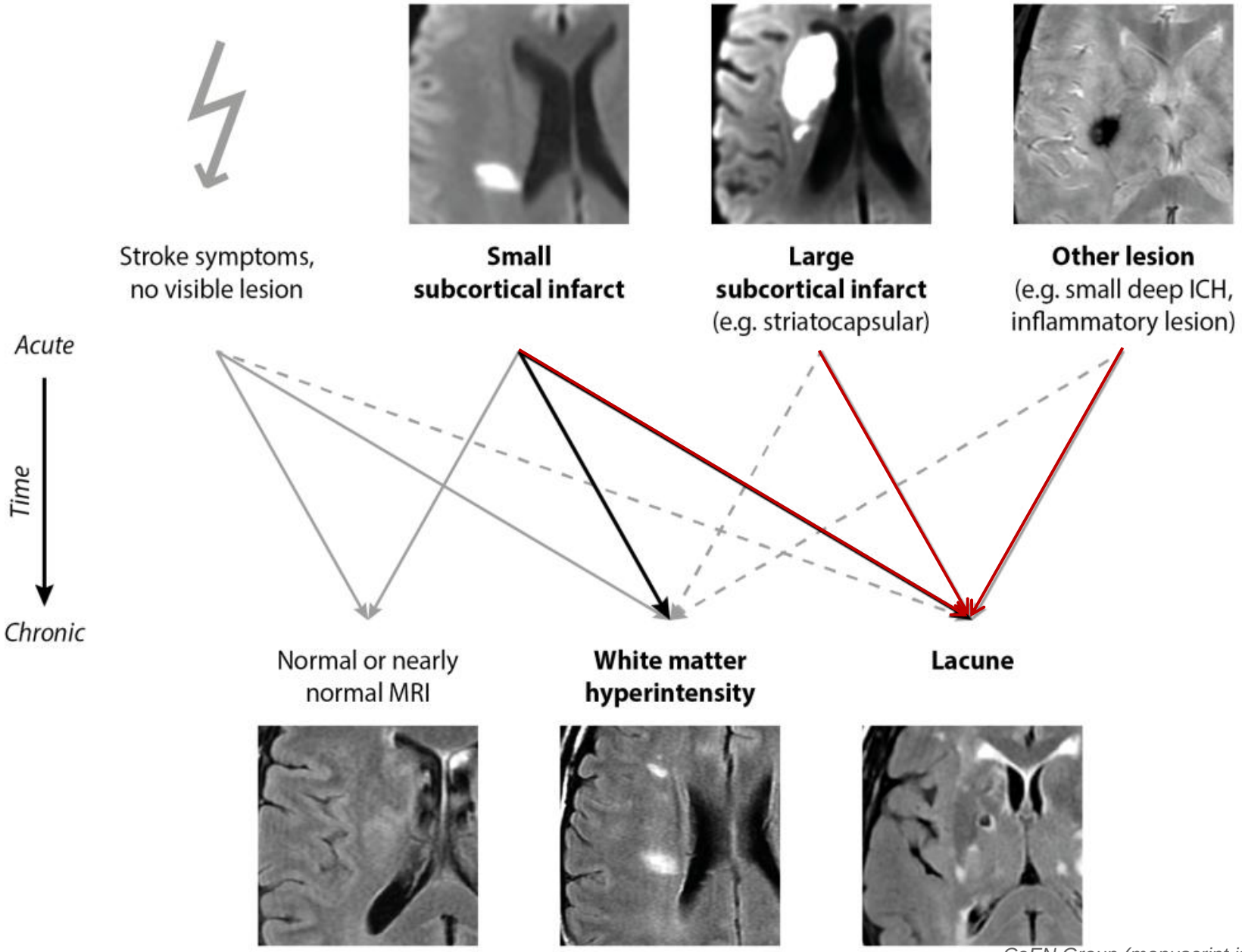
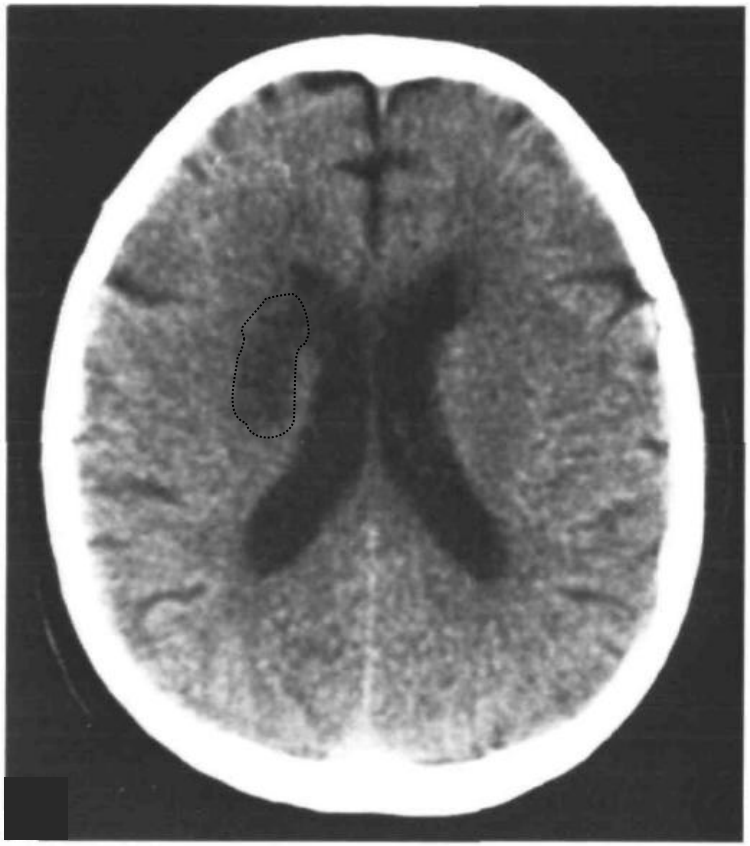


CoEN Group (manuscript in preparation)

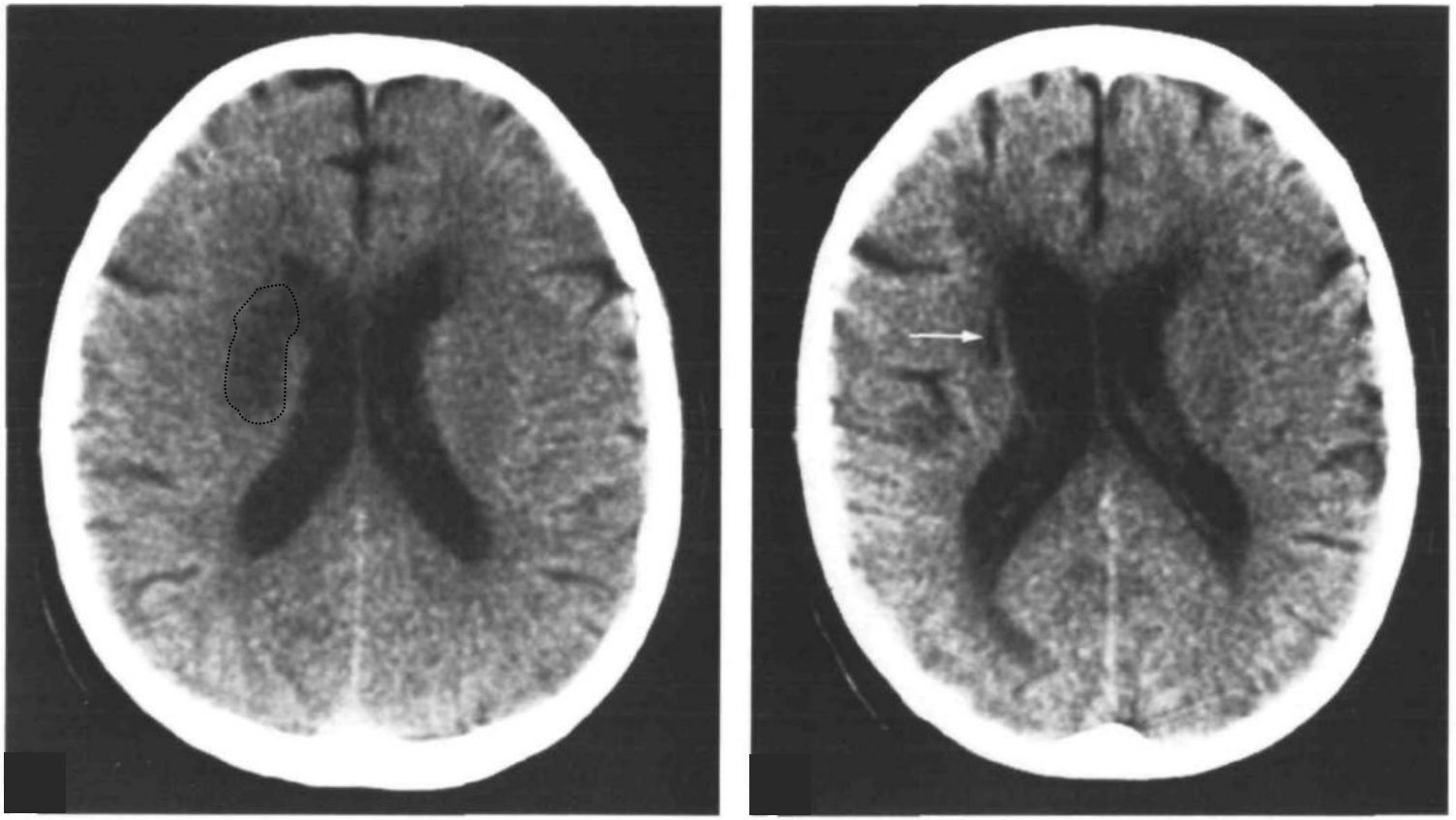
Striatocapsular Infarcts



G. Donnan Brain 1991

Striatocapsular Infarcts

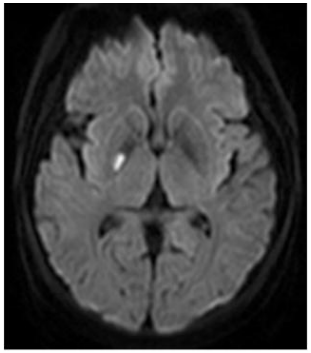
… typically collapse



follow-up

G. Donnan Brain 1991

Assumptions rather than Evidence
SVD Mimics on Neuroimaging



Largely Variable Terminology

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acute cerebral lacunar infarction
acute ischemic lacunar stroke
acute lacunar infarct(s)
acute lacunar infarction
acute lacunar motor syndrome
acute lacunar stroke
acute small deep brain infarcts
Acute small subcortical infarctions
acute subcortical infarct(s)
acute subcortical infarction(s)
acute subcortical ischemia
acute subcortical stroke
arteriolar lesions
asymptomatic lacunar lesions
asymptomatic lacunar stroke
brain lacunae
brain lacunar infarction
cerebral infarct
cerebral infarct of lacunar type
cerebral lacunar infarction
cerebral lacunar lesions
chronic cerebral lacunar infarction
covert brain infarcts
covert infarcts
chronic striatocapsular infarction
chronic striatocapsular infarction
clinical lacunar syndrome
deep infarct
deep lacunar lesions
etat crible
hyperacute lacunar infarct
hyperintense lacune
incidental silent infarcts
incidental silent strokes
infarcts of lacunar or larger size
infarct with lacunar characteristics
isolated lacunar infarct
lacuna
lacunae
lacunar acute stroke syndrome
lacunar area
lacunar arteriopathy
lacunar brain infarcts
lacunar brain infarction
lacunar cerebral infarction
lacunar clinical syndrome
lacunar infarct(s)
lacunar infarction(s)
lacunar ischaemic stroke
lacunar lesion(s)
lacunar motor syndrome
lacunar pattern of infarction
lacunar pontine infarct
lacunar recurrence
lacunar sized infarcts
lacunar small deep infarcts
lacunar state
lacunar stroke(s)
lacunar stroke subtype
lacunar syndrome
lacunar syndrome of presumed ischemic origin
lacunar syndrome stroke
lacunar syndrome with infarction
lacunar type infarcts
lacunar volume(s)
lacunar white matter infarcts
lacunas
lacune(s)
medial pontine lacune(s)
microinfarct(s)
microinfarction
microscopic infarct
Non-embolic, lacunary infarctions
old lacunar infarctions
old lacunar infarcts
old lacunes
perforator territory infarction
pontine infarction(s)
pontine lacunar syndromes
silent brain infarct(s)
silent brain infarction(s)
silent brain lesion(s)
silent cerebral infarct(s)
silent cerebral infarction
silent cerebral lacunar infarcts
silent cerebral lesions
infarcts
silent cerebral lesions
"silent" ischaemic brain lesions
silent ischaemic lesions
silent infarct
silent lacunar infarct(s)
silent lacunar infarction
silent lacune(s)
silent lesions
silent stroke
silent subcortical infarct
single small subcortical infarction(s)
small-deep asymptomatic infarction
small deep brain infarcts
small deep infarct(s)
small deep infarction(s)
small deep (lacunar) infarcts
small, deeply located brain infarcts
small, deep subcortical infarct
small, deep subcortical ischaemic stroke
small hyperacute infarcts
small scattered infarcts <1cm
small subcortical index lesions
small subcortical infarct(s)
small subcortical infarction
small subcortical ischaemic stroke
small subcortical lesions
small subcortical stroke(s)
small vessel disease stroke
small vessel stroke
striatocapsular infarct
striatocapsular infarction
subclinical brain infarct(s)
subclinical brain infarction
subclinical cerebral lacunar infarction
subclinical lacunar infarct(s)
subclinical lacunar infarction
subclinical magnetic resonance imaging brain infarct
subcortical brain infarcts
subcortical cerebral infarcts
subcortical cerebral infarction
subcortical cystic infarctions
subcortical infarct(s)
subcortical infarction
subcortical ischaemic infarct(s)
subcortical ischaemic infarction(s)
subcortical ischaemic lesion
subcortical ischaemic stroke(s)
subcortical lacunar infarct(s)
subcortical lacunar-type infarction
subcortical lacunar lesions

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Largely Variable Terminology

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Terms used previously to describe WMH of presumed vascular origin

Term	Variants of use of term	Use of term in titles and abstracts	
		Total No.*	%
leukoaraiosis	ischemic leukoaraiosis, subcortical leukoaraiosis	350	31
white matter lesions	MRI white matter lesions (WML), cerebral WML, T2 WML/WMLs, cerebrovascular WML, subcortical WML, WML of Binswanger's disease, cerebral WML of Binswanger's disease, confluent WML, intracranial WML	275	24
white matter hyperintensity	cerebral WMH, age-related WMH, brain WMH, MRI WMH	217	19
white matter changes	age-related cerebral white matter changes (WMC); age-related WMC, cerebral WMC, changes in white matter, age-related changes in WM	136	12
leukoencephalopathy	subcortical ischemic leukoencephalopathy	76	7
white matter disease	age-related white matter disease (WMD), cerebral WMD, subcortical WMD	45	4
white matter damage	age-related WMD,	5	0
ischemic/ ischaemic white matter disease	ischemic subcortical WMD, chronic ischemic cerebral WMD, subcortical ischemic WMD	4	0
other terms (N=9)		17	1

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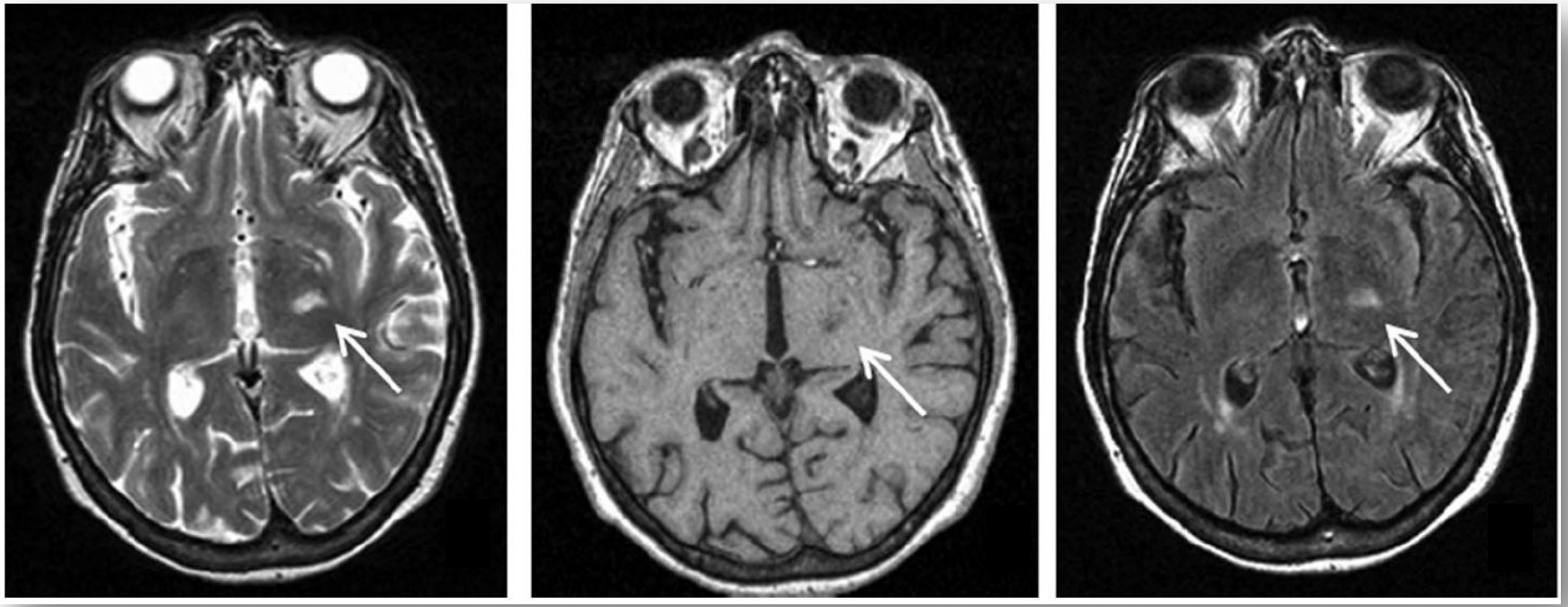
CoEN Group (manuscript in preparation)

How would you call this lesion?



A) lacunar infarct

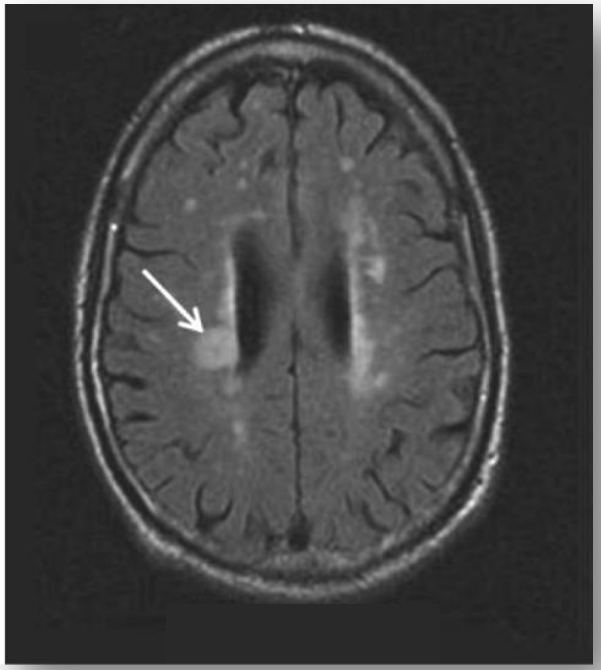
B) white matter lesion

C) lacunar lesion

D) basal ganglia infarct

E) other suggestion

How would you call this lesion?



A) stroke

B) lacunar infarct

C) white matter lesion

D) lacunar lesion

E) other

How would you call this lesion now?

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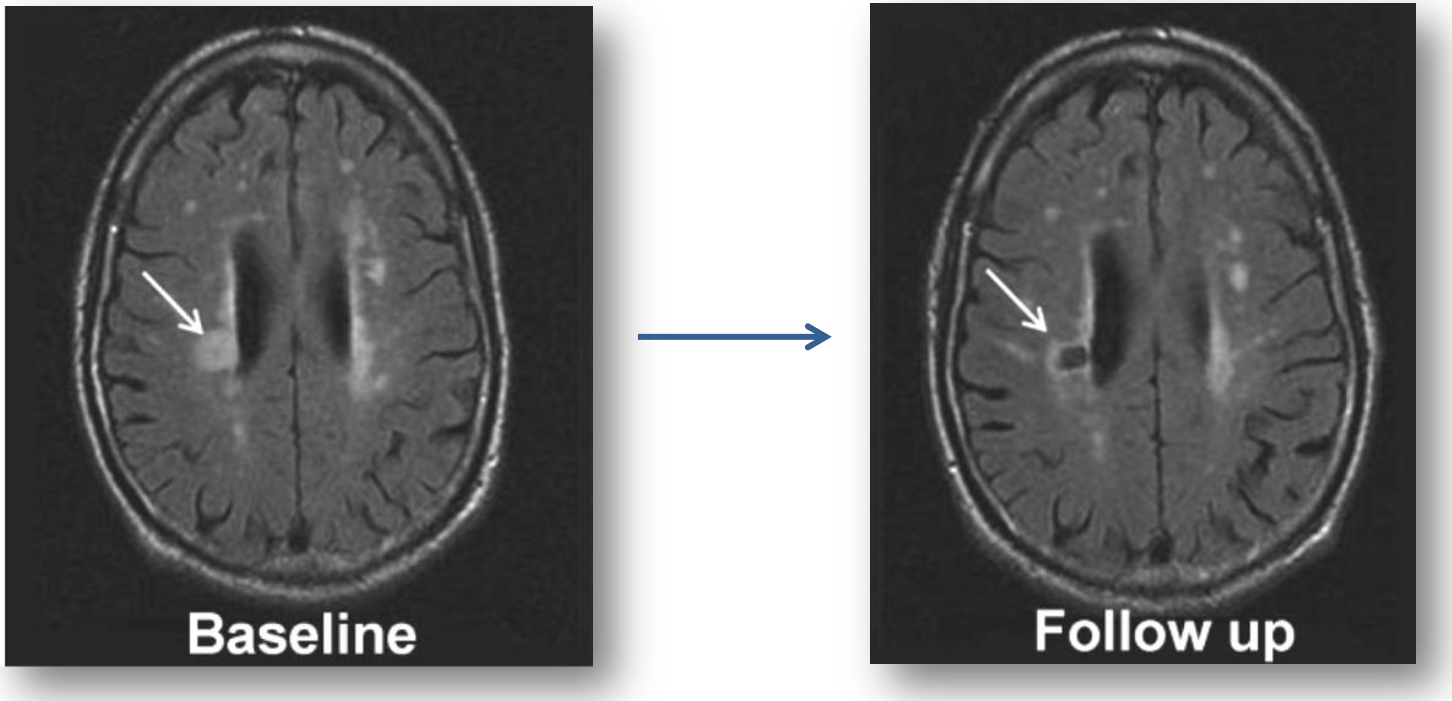


A) stroke

B) lacunar infarct

C) white matter lesion

D) lacunar lesion

E) other

A) stroke

B) lacunar infarct

C) white matter lesion

D) lacunar lesion

E) other

Different Terminologies Impede Scientific Progress

- cross-study comparisons
- meta-analyses
- research on risk factors
- pathophysiology,
- pathological correlations
- clinical consequences

- therapeutic progress

Recently Developed Standards

- U.S. National Institute of Neurological Disorders and Stroke (NINDS) and Canadian Stroke Network (CSN)
  Vascular Cognitive Impairment Harmonization Standards
  (Hachinski et al. Stroke 2006)

- Scientific Statement for Health Care Professionals from AHA / ASA on
  Vascular Contributions to Cognitive Impairment
  (Gorelick et al. Stroke 2011)

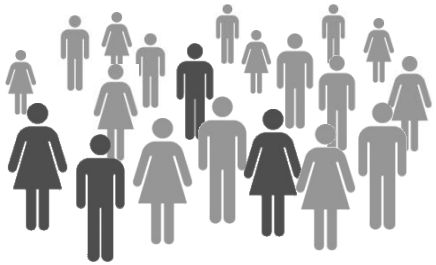
  > **class II recommendation** for neuroimaging as part of work-up for VCI

Why Standards for Imaging of SVD and Why Now?

- MR has become imaging standard in most research settings
- advances in image acquisition
- major progress in image post-processing
- recognition that harmonizing imaging and analytical protocols will facilitate pooling of data, performing meta-analyses, and cross-study comparisons
- growing appreciation of the impact of vascular factors in neurodegeneration but also in other conditions

CoEN Process & Milestones

additional experts
to join working groups



preparation workshop

- set the scene
- agree process
- define work packs
- assemble groups
- get started

1st workshop

work package 1

work package 2

work package 3

work package x

- present work pack.s
- discuss
- modify
- consent
- disseminate

2nd workshop

manuscript preparation

conference dissemination

Mar 2012

Nov 2012

2013.....

CoEN Process | Participants

Working Groups:

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M. Dichgans (DZNE)
E. Smith (CSN)
H. Chabriat
N. Fox (MRC)
J. O'Brien (MRC)
D. Werring (MRC)
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O. Benavente (CSN)
R. Frayne (CSN)
B. Stephen (MRC)
V. Hachinski (CSN)
S. Greenberg (AHA / ASA)
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G.J. Biessels
P. Gorelick (AHA / ASA)
C. Cordonnier
L. Pantoni
R. Lindley
A. Viswanathan
R. Van Oostenbrugge
F. Barkhof
F. Fazekas
O. Speck (DZNE)
V. Mok

Observers:

P. Gorelick (AHA / ASA)
B. Norrving (ESO / WSO)
D. Leys (ESO)
C. DeCarli (AA)
C. Chen
M. Van Buchem
A. Hakim (CSN)
C. Smith (MRC)

Others:

I. Kiliman (DZNE)
M. Düring (ISD/DZNE)
M. Ewers (ISD)

DZNE = German Center for Neurodegeneration; CSN=Canadian Stroke Network; AHA/ ASA=American Heart Association / American Stroke Association; ESO=European Stroke Organization; WSO=World Stroke Organization; AA=Alzheimer Association)

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COEN | Working principles

Terminology – intuitive,

Avoid - new terms (where possible; terms that imply specific presumed (yet unknown) pathology; ambiguous terms

Harmonisation, reduce to common denominator

Is there a reason for multiple terms that we should observe?

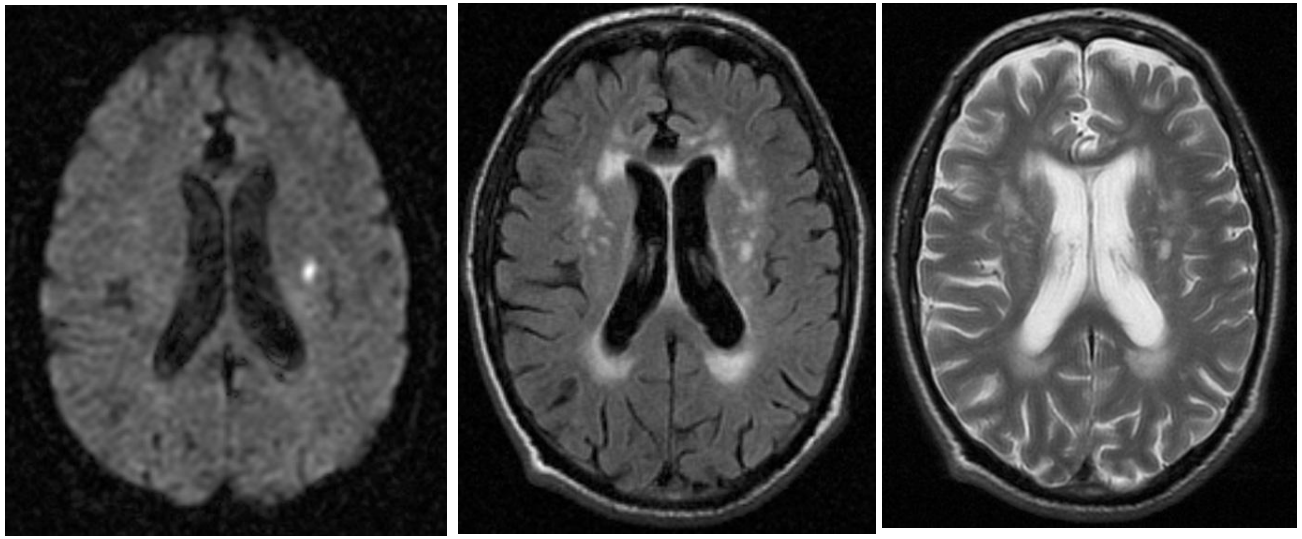
Consensus – has to be the widest possible

Nuances count – disciplinary, cultural and language barriers

Keep it simple

Can’t fit a square peg in a round hole!

recent small subcortical infarcts

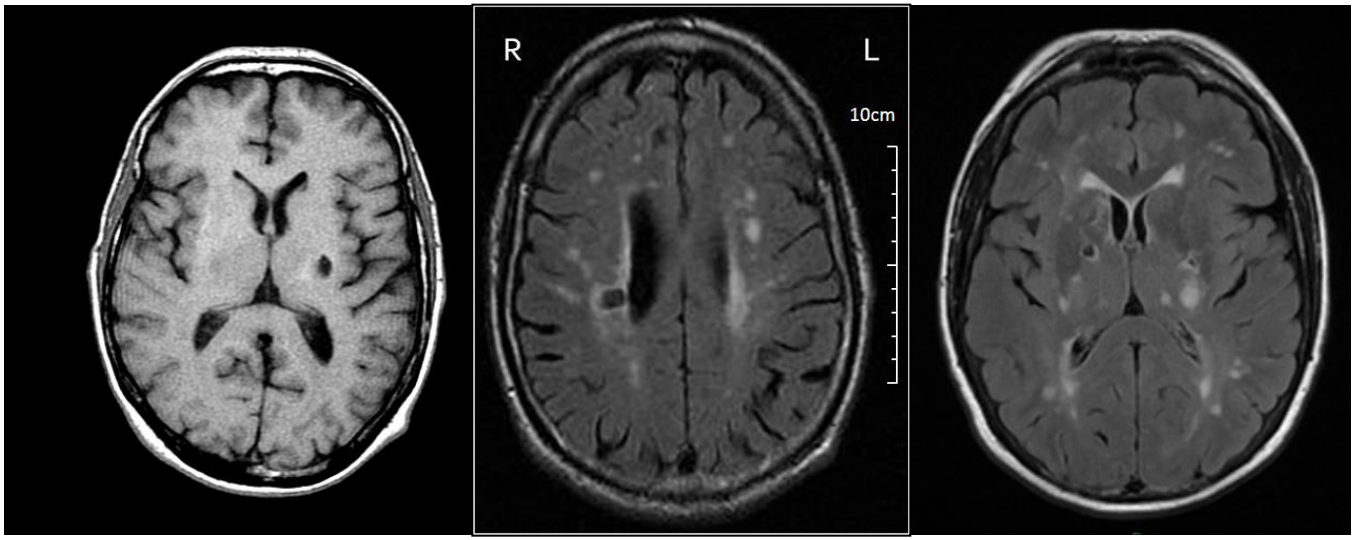


Working Group:

- JM Wardlaw
- R. van Oostenbrugge
- V. Hachinski
- B. Stephan
- V. Mok
- L. Pantoni
- F Doubal

"Recent small subcortical infarct : neuroimaging evidence of recent infarction in the territory of a single perforating arteriole, with imaging features or correlating clinical features consistent with a lesion occurring in the last few weeks."

Lacunes of Presumed Vascular Origin

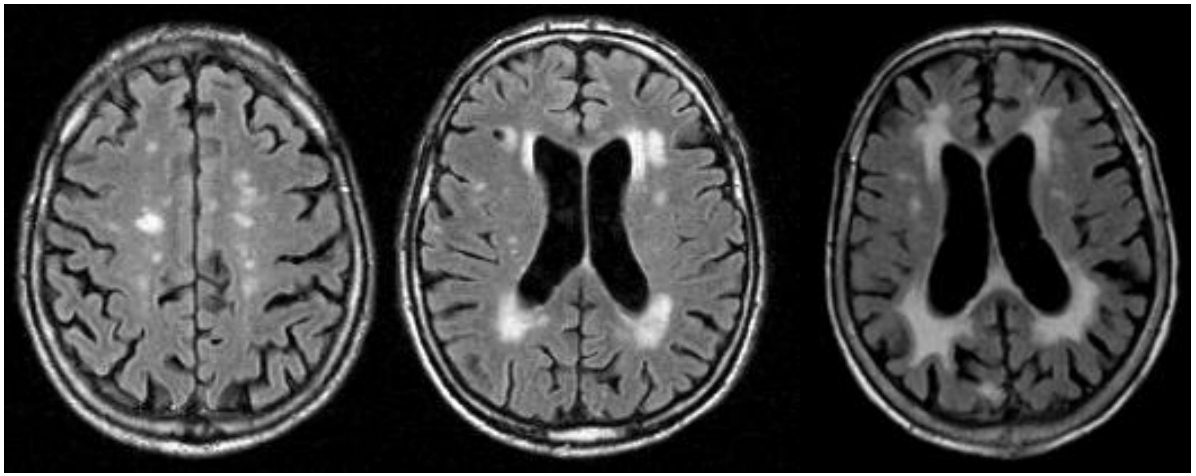


Working Group:

- Richard Lindley
- Hugues Chabriat
- Monique Breteler
- Carol Brayne
- Vincent Mok
- Oscar Benavente

"Round or ovoid, subcortical, fluid filled (similar signal to CSF) cavity between 3 and about 15 mm in diameter, compatible with a previous acute small deep brain infarct or haemorrhage, in the territory of one perforating arteriole."

White Matter Hyperintensities of Presumed Vascular Origin



Working Group:

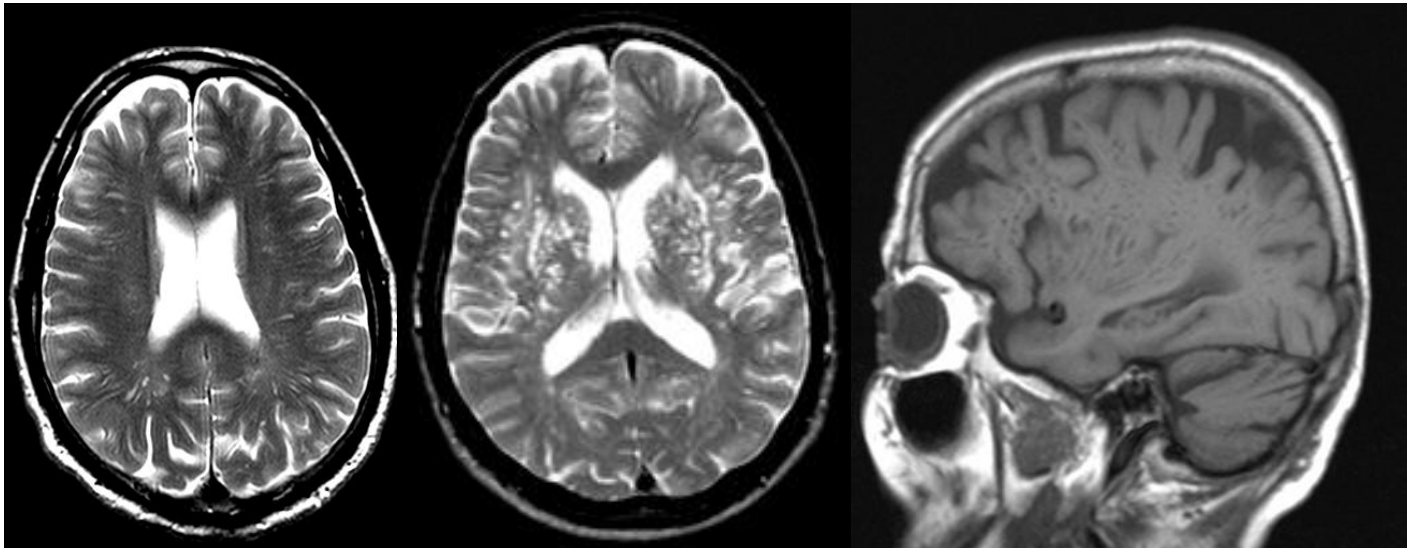
- Charlotte Cordonnier
- Frank-Erik de Leeuw
- Charles DeCarli
- Franz Fazekas
- John O'Brien
- Sandra Black
- Leonardo Pantoni

"Signal abnormality of variable size in the white matter showing the following characteristics:

Hyperintense on FLAIR and T2/PD-weighted images without cavitation (signal different from CSF).

Lesions in the subcortical gray matter or brain stem are not included into this category unless explicitly stated. "

Perivascular Spaces (PVS)

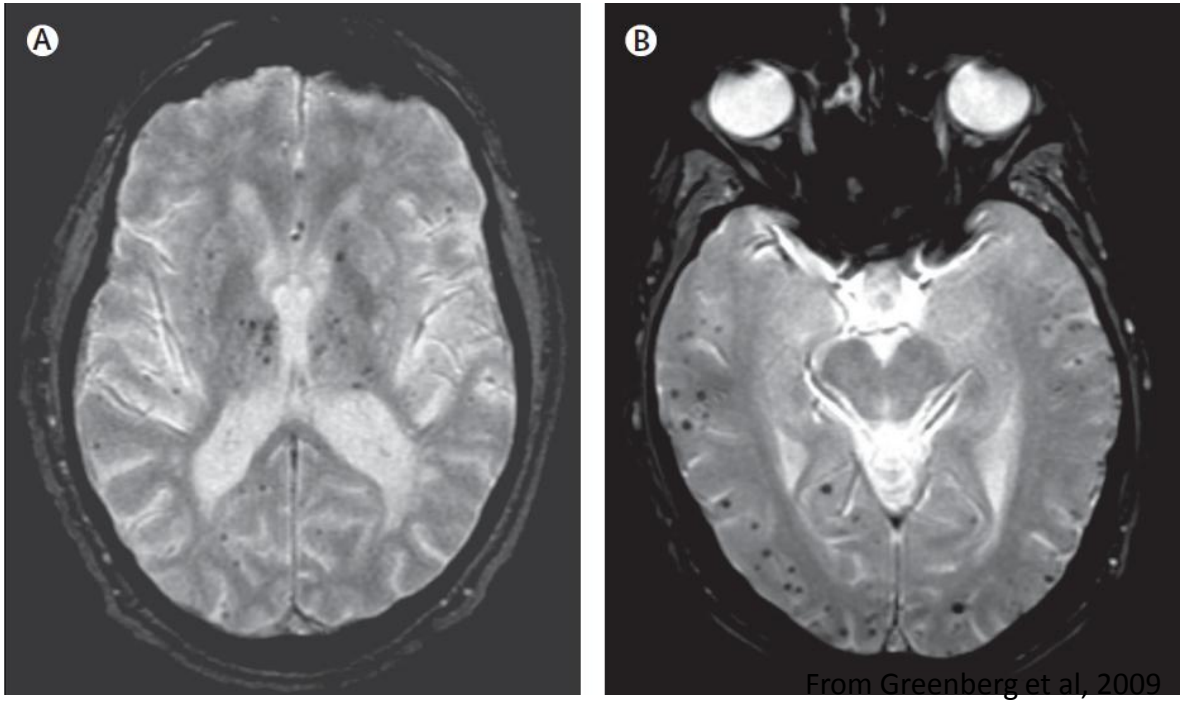


Working Group:

- F. Fazekas
- A.Viswanathan
- R.Ooostenbrugge
- G.J.Biessels
- V.Hachinski
- F.Barkhof

"Fluid filled space that follow the typical course of a vessel as it goes through grey or white matter. The spaces have signal intensity similar to CSF on all sequences. Because they follow the course of penetrating vessels, they appear linear when imaged parallel to the course of the vessel, and round or ovoid, with a diameter generally smaller than 3 mm, when imaged perpendicular to the course of the vessel."

Cerebral Microbleeds



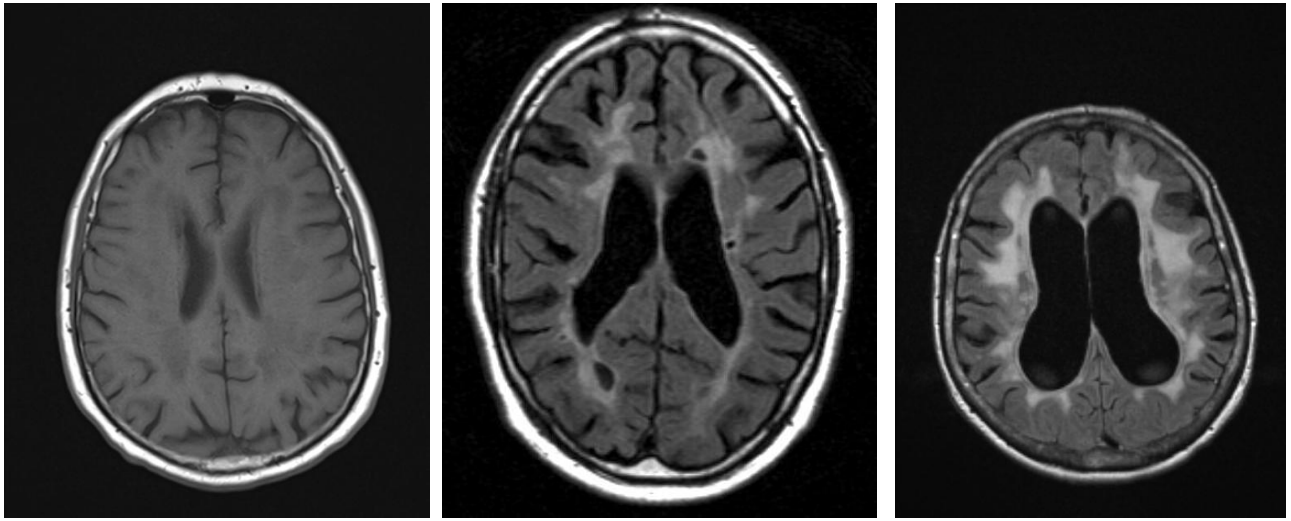
From Greenberg et al, 2009

Working Group:

- John O'Brien
- Monique Breteler
- Charlotte Cordonnier
- Richard Frayne
- Richard Lindley
- David Werring

Small (generally 2-5 mm, but sometimes up to 10 mm) areas of signal void with associated "blooming" seen on T2*-weighted MRI or other sequences that are sensitive to susceptibility effects.

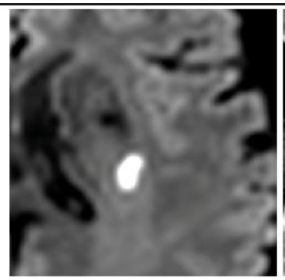
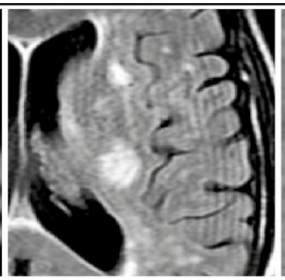
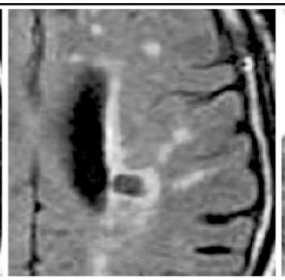
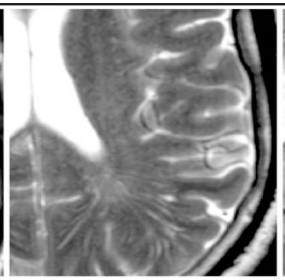
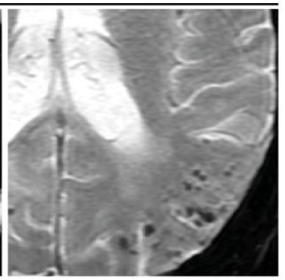
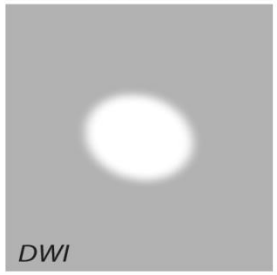
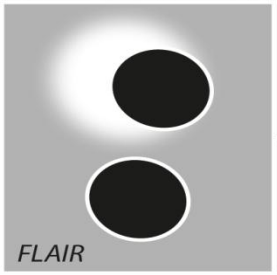
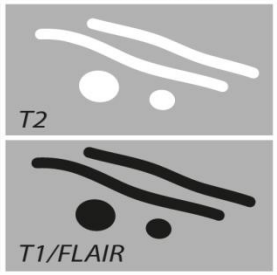
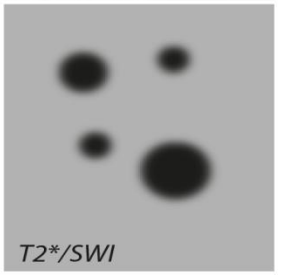
Brain Atrophy



Working Group:
- G-J Biessels
- N Fox
- I Kilimann
- S Greenberg
- S Teipel
- S Black
- F Barkof

A decreased brain volume that is not related to a specific macroscopic focal injury such as trauma or infarction. Thus, infarction is not included in this measure unless explicitly stated

STRIVE: Standards for Reporting and Imaging of Small Vessel Disease

	Recent small subcortical infarct	White matter hyperintensity	Lacune	Perivascular space	Cerebral microbleeds
Example image					
Schematic					
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)	↔	↓↓

Standards for Imaging of SVD | Other Outputs

Additionally, suggestions for:

- Image acquisition protocols: brief (10 minutes), standard clinical (30 minutes) and research options
- Principles of MRI image analysis
- Standards for reporting of studies

CASES

CASE: A FORGETFUL MAN

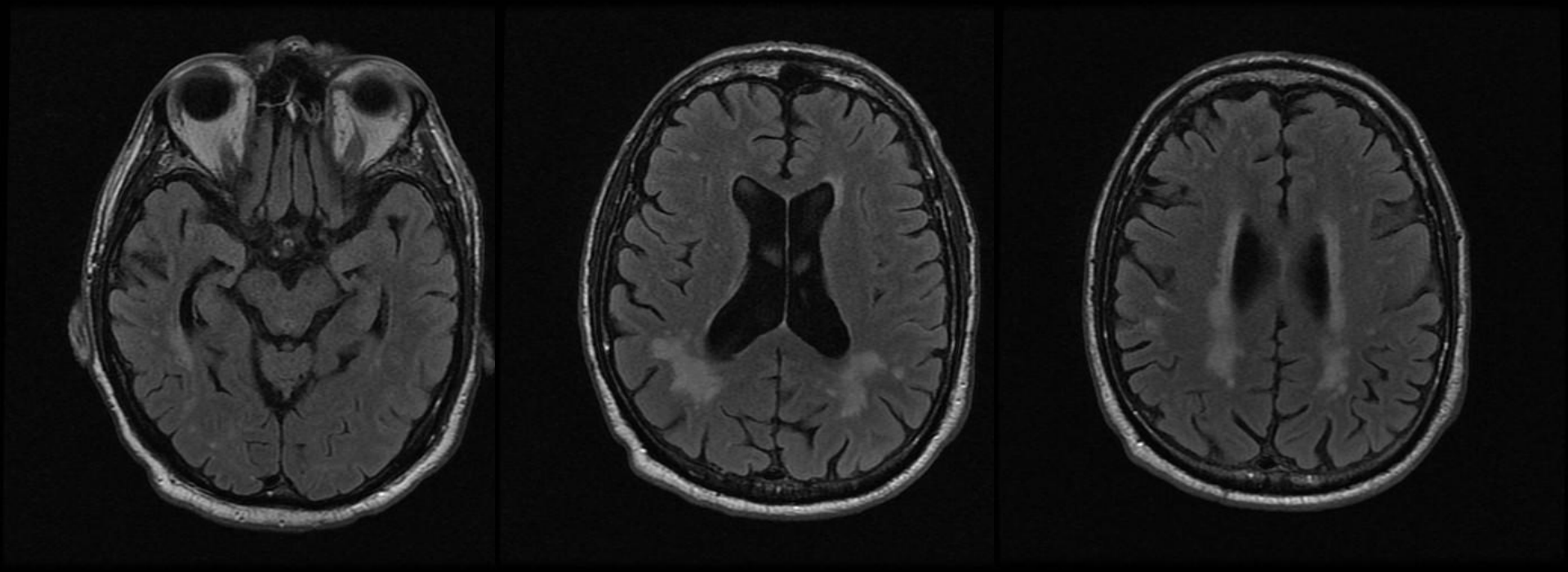
- 73 man.
- First seen in June 2011 with forgetfulness, apathy, decreased motivation.
- Gets grocery items incorrectly (e.g. Lasagna instead of spaghetti noodles).
- Still drives, shops, does personal finances.
- CT report faxed to clinic describes “moderate burden of ischemic white matter disease”.
- PMH: benign prostatic hypertrophy, insomnia.
- Medications: L tryptophan, Flomax, Avodart, and vitamins.
- Normal score on Addenbrooke’s.

CASE 1: FOLLOW UP JULY 2012

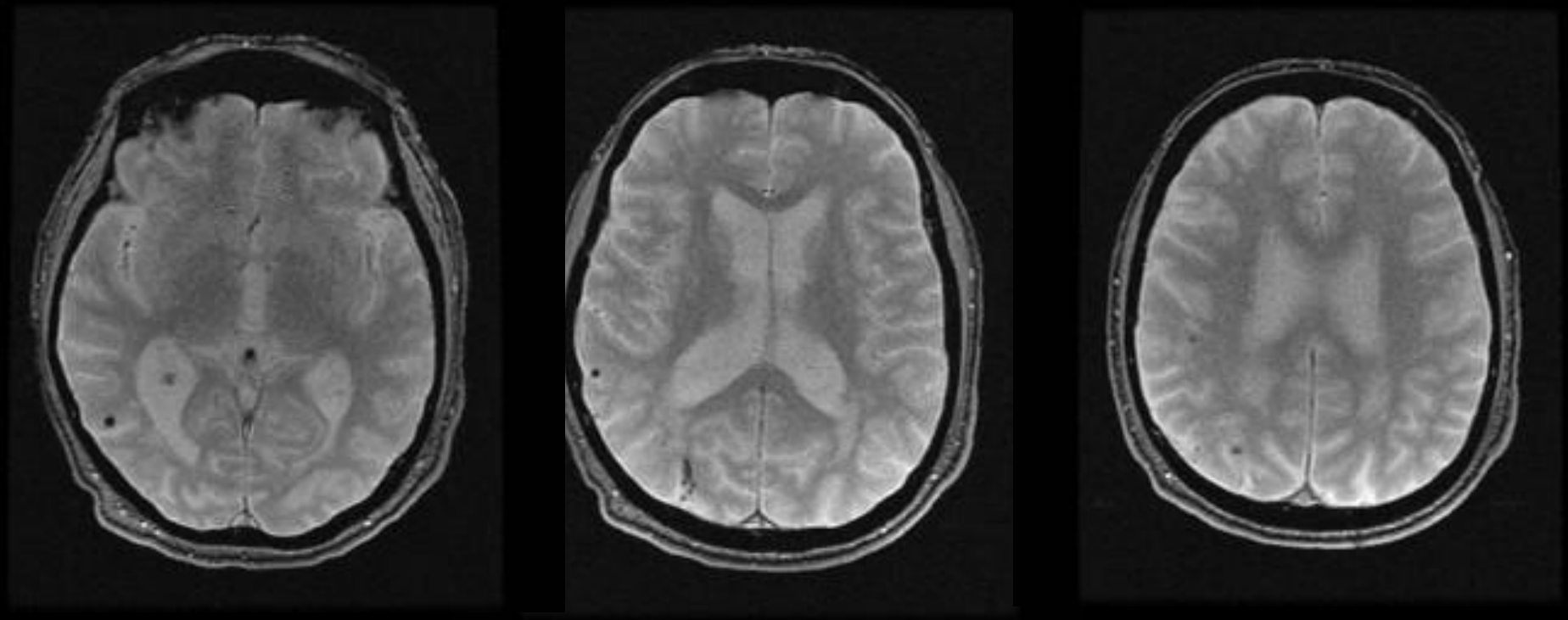
- Patient and wife endorse continued cognitive concerns; wife is very distraught.
- ADL essentially preserved but hired an accountant for the first time to help with taxes.
- MMSE: 30/30.
- MoCA: 24/30.
- Geriatric Depression Scale: 4/15.
- Neuropsych testing:
  - CVLT long delay free recall: -1.0 SD
  - Trails B: -1.0 SD
  - COWAT, Clock drawing, Trails A

Diagnostic impression?

MRI FLAIR



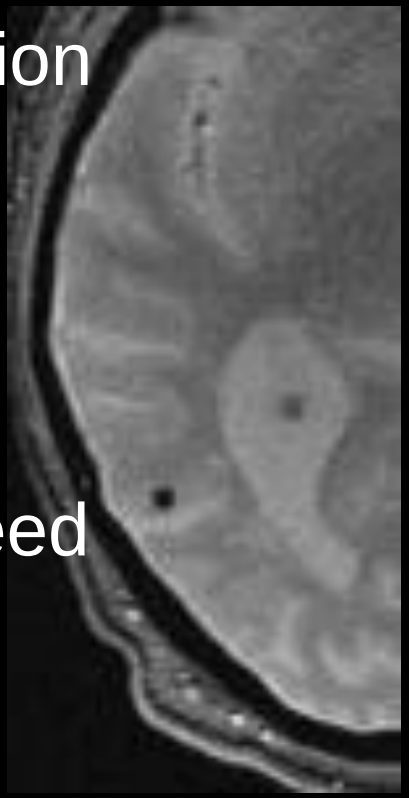
MRI T2*-weighted Gradient-Recalled Echo



BEWARE MICROBLEED MIMICS

Blood vessel

in cross-section



Microbleed

Also beware

- Calcification, particularly in basal ganglia.
- Superficial siderosis (pathological).
- Susceptibility artifact at base of brain.

Diagnosis?

1. Vascular MCI
2. Caused by CAA?

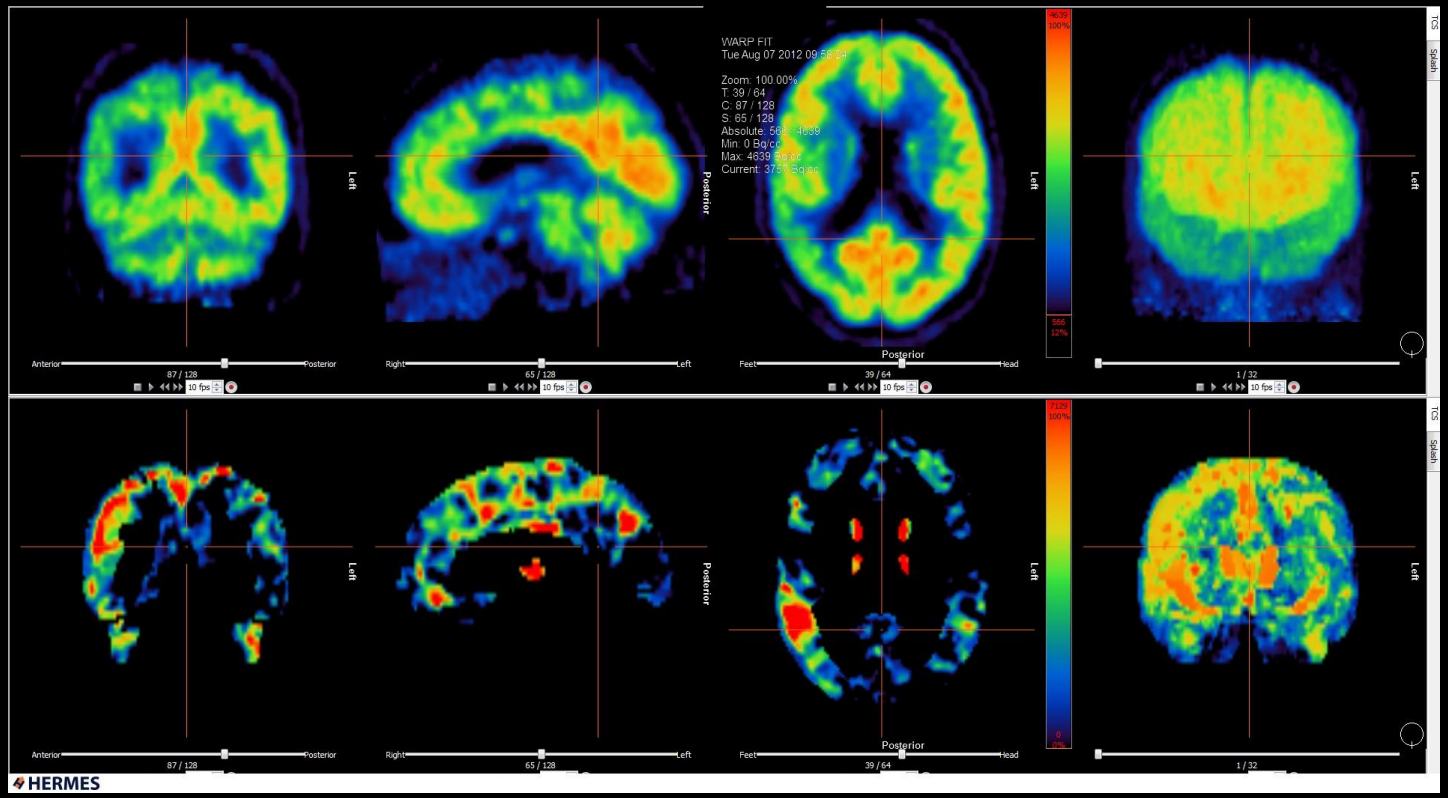
COGNITIVE IMPAIRMENT IN CAA

- Cognitive impairment in CAA could be due to:
  - Effects of stroke.
  - Concomitant AD pathology.
  - Effects of CAA independent of stroke, potentially mediated by WMH, microinfarcts or blood flow dysregulation.

FDG PET

FDG

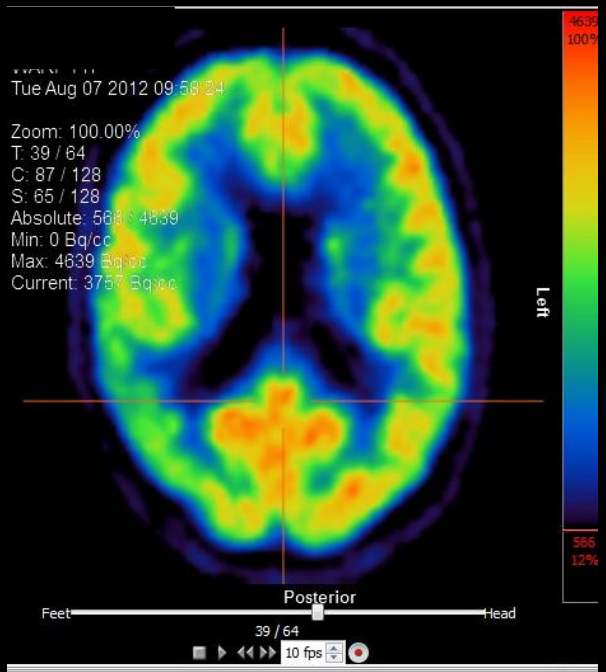
Difference From Normal

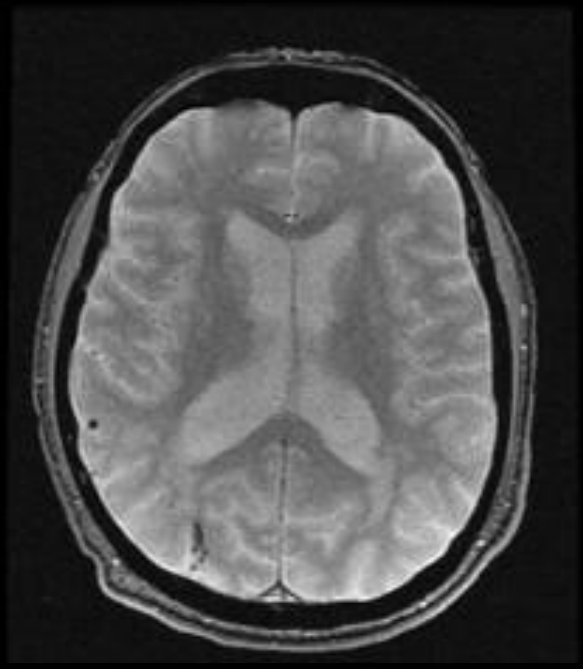


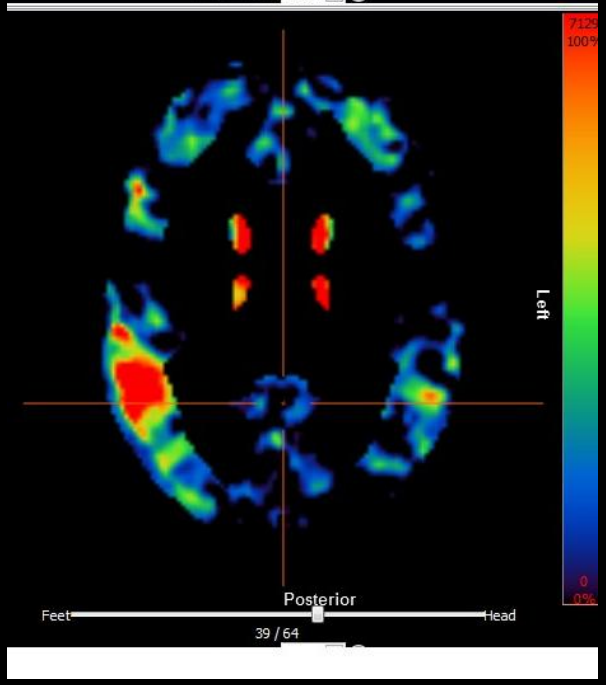
FDG PET

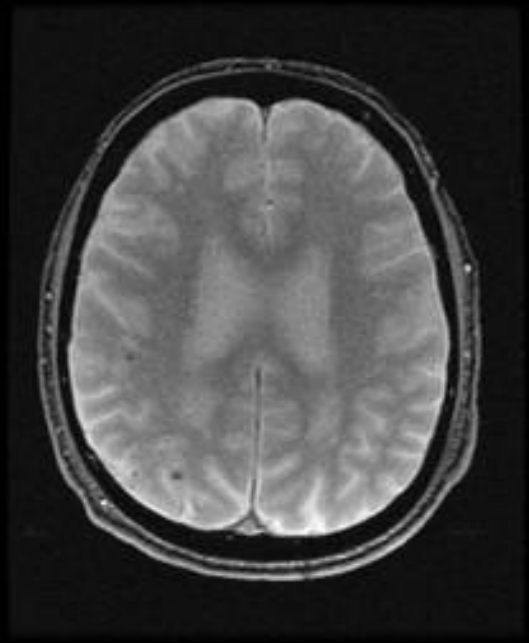
FDG

Difference From Normal









PET INTERPRETATION

- Hypometabolism in right parietal > frontal lobe.
- Normal metabolism in areas typically affected by AD: temporal lobe, posterior cingulate gyrus.
- Radiological diagnosis: vascular disease, unlikely to be AD.

FINAL DIAGNOSIS

Vascular MCI probably caused by CAA

CAA

- Caused by beta-amyloid deposition in the medial and adventitia of small arteries of the cortex and leptomeninges.
- Clinical manifestations: lobar intracerebral hemorrhage, sulcal subarachnoid hemorrhage, transient neurological symptoms, cognitive impairment.
- Neuroimaging manifestations: microbleeds, macrobleeds, superficial siderosis, WMH, abnormal DTI, decreased fMRI activity, small infarcts.
- Management:
  - No specific disease modifying therapies.
  - Lowering blood pressure may help prevent recurrent stroke.
  - **Avoid antithrombotics!** Hemorrhagic stroke risk on average is 5-10% per year, up to 15% per year in patients with symptomatic stroke and multiple microbleeds (>5).

DIAGNOSIS OF CAA (Lin et al, Neurology 2010

Table 1 Classic and modified Boston criteria for CAA-related hemorrhage

	Classic Boston criteria[2]	Modified Boston criteria
Definite CAA	Full postmortem examination demonstrating:	No modification[a]
	• Lobar, cortical, or corticosubcortical hemorrhage	
	• Severe CAA with vasculopathy	
	• Absence of other diagnostic lesion	
Probable CAA with supporting pathology	Clinical data and pathologic tissue (evacuated hematoma or cortical biopsy) demonstrating:	No modification[a]
	• Lobar, cortical, or corticosubcortical hemorrhage	
	• Some degree of CAA in specimen	
	• Absence of other diagnostic lesion	
Probable CAA	Clinical data and MRI or CT demonstrating:	Clinical data and MRI or CT demonstrating:
	• Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed)	• Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) or
	• Age ≥55 y	• Single lobar, cortical, or corticosubcortical hemorrhage and focal[b] or disseminated[c] superficial siderosis
	• Absence of other cause of hemorrhage	• Age ≥55 y
		• Absence of other cause of hemorrhage or superficial siderosis
Possible CAA	Clinical data and MRI or CT demonstrating:	Clinical data and MRI or CT demonstrating:
	• Single lobar, cortical, or corticosubcortical hemorrhage	• Single lobar, cortical, or corticosubcortical hemorrhage or
	• Age ≥55 y	• Focal[b] or disseminated[c] superficial siderosis
	• Absence of other cause of hemorrhage	• Age ≥55 y
		• Absence of other cause of hemorrhage or superficial siderosis

Abbreviation: CAA = cerebral amyloid angiopathy.

CASE: SLOWED COGNITION AND GAIT

- 59 man.
- Cognitive slowing, forgetfulness. Gait slow.
- PMH: previous stroke in 2001 with temporary R weakness, resolved.
- Family hx: father died at 78, mother alive at 85 without dementia.
- Aricept 5 mg/d.
- Mild hyper-reflexia, couple of beats clonus at ankles, unable to tandem walk.
- MMSE 21, MoCA 14.
- BP 124/77. P 82. BMI 20.
- TSH, B12, homocysteine normal.
- LP: no cells, VDRL negative, no oligoclonal bands

SUBSEQUENT COURSE

2010

- MoCA 14. Takes bus to appointment.

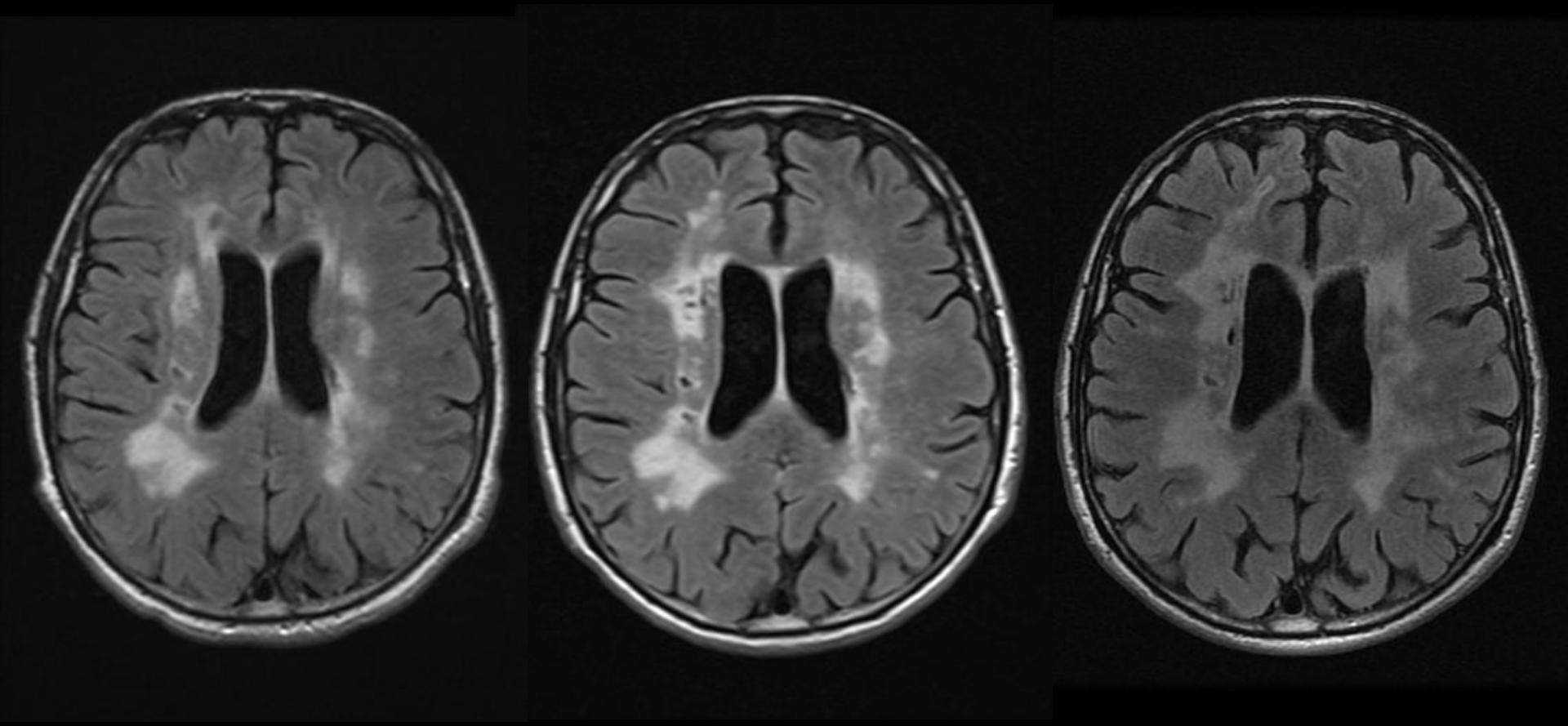
2011

- MoCA 13.
- Worse forgetfulness, weight loss
- Wide-based, unsteady gait, en-bloc turning.
- CADASIL negative.

2013

- MMSE 11/30. BP 97/59.
- Worse forgetfulness, mostly confined to wheelchair, urinary urgency.

MRI FLAIR

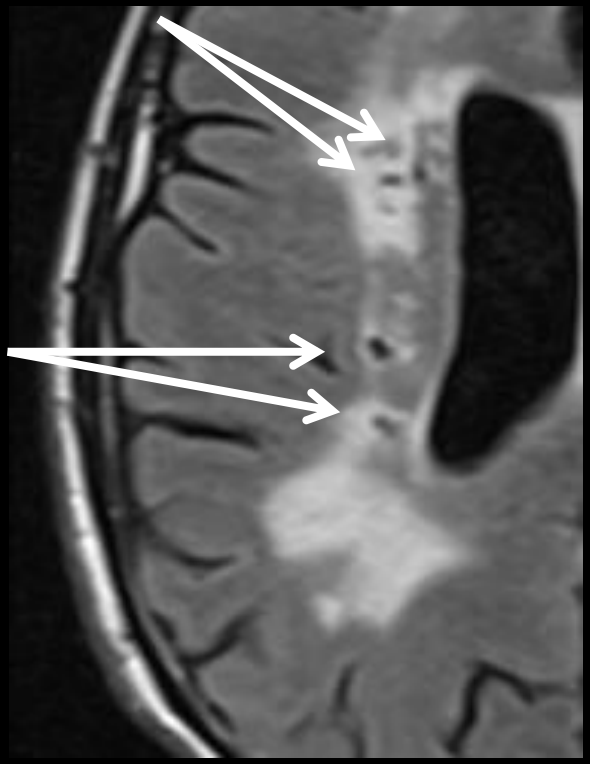


2007 2009 2011

IS IT A LACUNE?

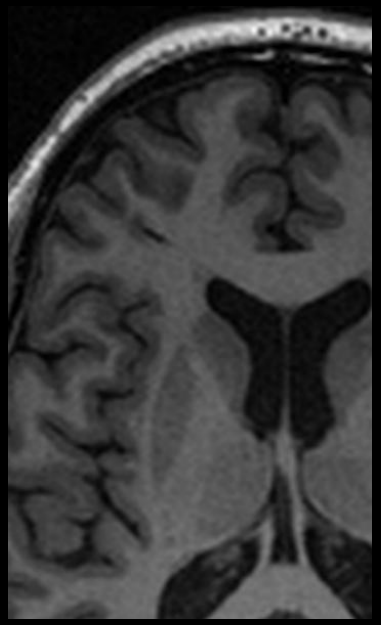
Discriminating lacunes from PVS

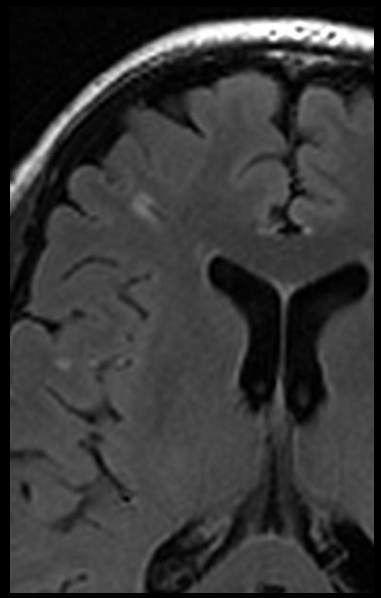
Perivascular space?



Lacune

>3 mm





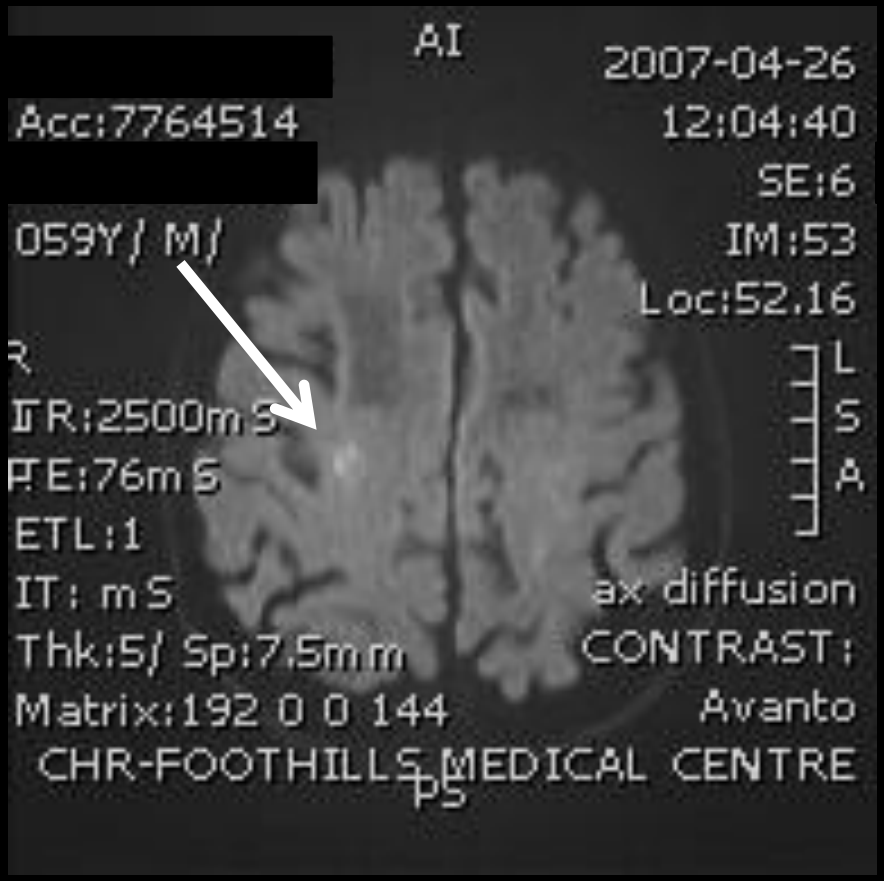
Criteria

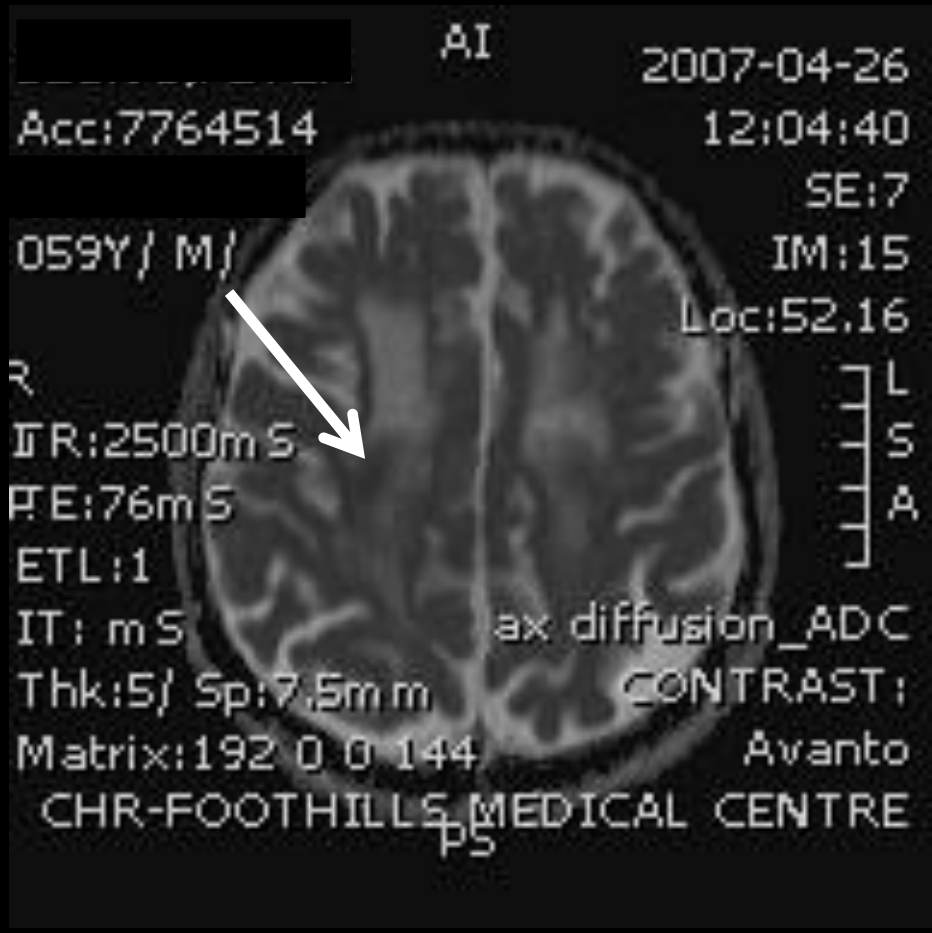
-Shape

-Size

-Location

MRI DWI





Incidental recent small subcortical infarct

Diagnosis?

Probable Vascular Dementia, Subcortical Type

Not associated with traditional vascular risk factors, cause unclear