63 yo RH Caucasian male

- Presents 10/08 with three brief spells of slurred speech
- No health care for decades but BP was elevated when basal cell ca excised 1 year ago
- NIHSS 0
- BP 242/106
- MRI: moderate chronic white matter signal hyperintensities in the cerebral hemispheres and brainstem
• After admission fluctuating R facial droop, slurred speech and pure motor R hemiparesis

• At 24 hours after admission the right arm and leg were completely flaccid, speech severely dysarthric NIHSS: 13

• BP's ranged 103-208 systolic

• Echo: severe concentric LVH

• TC: 162, HDL: 43, LDL: 120, Trig: 63

• Hgb A1c: 5.7
DWI: 1 day after admission

DWI: day of admission
STROKE

Primary Hemorrhage
15%
  - intraparenchymal
  - subarachnoid

Ischemic Stroke
85%

Atherosclerosis
20%
  - thrombosis
  - arteriogenic emboli

Small Artery Disease
25%
  "lacunes"

Cardiogenic Embolism
20%
  - atrial fibrillation
  - many others

Cryptogenic Stroke
30%
  - ? aortic emboli

Other, Unusual Causes
5%
  - dissections, arteritis, migraine
  - hypercoagulability, drug abuse, more
Thrombotic & Embolic Stroke
Sites of Atherosclerosis

- Especially above bifurcations
- At sites of maximum turbulence and sheer stress
Inflammation & Atherosclerosis

Figure 1. Endothelial Dysfunction in Atherosclerosis.

Figure 2. Fatty-Streak Formation in Atherosclerosis.

Figure 3. Formation of an Advanced, Complicated Lesion of Atherosclerosis.

Figure 4. Unstable Fibrous Plaques in Atherosclerosis.
Atherosclerosis Timeline

- **Endothelial Dysfunction**
  - Foam Cells
  - Fatty Streak
  - Intermediate Lesion
  - Atheroma
  - Fibrous Plaque
  - Complicated Lesion/Rupture

- **From first decade**: Growth mainly by lipid accumulation
- **From third decade**: Smooth muscle and collagen
- **From fourth decade**: Thrombosis, hematoma
Area at Risk

Lodged blood clot
Deep penetrating small vessels

Temporal cortex
Old lacunar Strokes (Lacunae)
Right Caudate & Putamen
Lacunar infarcts: thalamus
Lacunar Infarcts Pons
• Meticulous dissections of lacunar strokes (LS)
• 1950-1960’s
• Described classic lacunar stroke syndromes
• Most LS found distal to occlusive lesions of small perforating arteries
• “Lipohyalinosis”—he believed due to hypertension: fibrinoid necrosis and segmental arteriolar disorganization
• 3 overlapping findings:
  • Vessel enlargement
  • Hemorrhage
  • Fibrinoid deposition

C. Miller Fisher
Common Lacunar Stroke Syndromes

- pure motor hemiparesis
- pure hemisensory loss
- clumsy hand/dysarthria
- crural hemiparesis/ataxia

- May evolve over 24-72 hours
- “Stroke in Evolution”
63 yo RH Caucasian Male

- Fluctuating R hemiparesis
- Treated with reclined bed rest, aspirin, atorvastatin
- Improved over next 24 hours: NIHSS stabilized at 3-4 (down from 13 at worst)
- Treatment of BP started several days after stabilization
- Ambulatory, marginal dysarthria and using RUE though fingers slightly clumsy at d/c
STRIVE Criteria

STandards for Rепorting Vascular Changes on NEuroimaging

• Published 2013

• 36 authors
White Matter Hyperintensities of presumed Vascular Origin

Lacunes
Enlarged Perivascular Spaces

Microbleeds
Recent Small Subcortical Infarcts

Brain Atrophy

Cortical Microinfarcts
A. Evolution into a WMH

B. Evolution into a lacune

C. Evolution into a cavity with hemorrhagic component
Joanna M Wardlaw MD, Edinburgh

William M Feinberg Award for Excellence in Clinical Stroke 2018
Small vessel disease IS NOT just atherosclerotic disease in little vessels
Figure 7: MRI of cerebrovascular endothelial permeability

Top row: 56-year-old patient with a right thalamic lacunar infarct. (A) Diffusion-weighted imaging. (B) FLAIR 2 days after symptom onset. (C) 2 months later, FLAIR image after intravenous gadolinium showing gadolinium in the perivascular spaces (D; arrowheads) and sulci (arrows) and (D) inset magnified image of (C). Bottom row: older patient with left internal capsule lacunar infarct (not shown). (E) Colour mapping of cerebrovascular permeability after intravenous gadolinium and (F) corresponding FLAIR images showing white matter hyperintensities. Blue shows low cerebral vascular endothelial permeability, yellow and red show increasing permeability. Permeability changes are diffuse. (G) Permeability and (H) corresponding FLAIR image on the slice adjacent to (E) and (F). Panels E and G courtesy of Dr Maria Valdes Hernandez. FLAIR=fluid-attenuated inversion recovery.
Transcranial Doppler

- No evidence for decreased resting cerebral blood flow beyond that expected from tissue damage
- Decreased MCA vasoreactivity with advancing age is greater with LS or WMI
- Increased vessel pulsatility
- Combination of impaired cerebrovascular vasoreactivity and increased vessel stiffness contributes to endothelial dysfunction
SVD Evolution

- Diffuse endothelial injury occurs early
- Leads to breakdown of the “Blood Brain Barrier”
- Extravasation of plasma proteins
- Injury to blood vessel wall, surrounding cells — especially glia (demyelination), inflammation, glial scarring, thickening and stiffness of the vessel wall, impaired autoregulation
- Late luminal narrowing & occlusion
What is the Glymphatic System?
Figure 4: Examples of visible perivascular spaces on MRI and histology
(A) 72-year-old asymptomatic patient, T2-weighted image (right) shows linear visible perivascular spaces in the plane of the image, and FLAIR (left) shows white matter hyperintensities around the perivascular spaces.
(B) T2-weighted imaging of a 49-year-old man with left internal capsule acute small deep infarct (not shown) shows a perivascular space extending from the periventricular to subcortical tissues and (C) on the corresponding FLAIR image, one white matter hyperintensity running longitudinally around the visible perivascular spaces.
(D) Visible perivascular spaces on histology showing parenchymal tissue retraction from around small perforating vessels; these have been dismissed as a processing artifact but are typically seen in ageing brain sections, and are often associated with cerebral small vessel disease. FLAIR=fluid-attenuated inversion recovery. H&E=haemotoxylin and eosin staining.
What is the Blood Brain Barrier?
A Measured simultaneously in the head:

- Resting CBF
- Pulsatility ↑
- Vasoreactivity ↓

B Effect on WMH and PVS:

- WMH ↑
- No association with resting CBF
- Vasoreactivity ↓
- PVS

C WMH form around PVS:
SVD Evolution

- Diffuse endothelial injury occurs early
- Leads to breakdown of the “Blood Brain Barrier”
- Extravasation of plasma proteins
- Injury to blood vessel wall, surrounding cells — especially glia (demyelination), inflammation, glial scarring, thickening and stiffness of the vessel wall, impaired autoregulation
- Late luminal narrowing & occlusion
Cerebral small vessel disease

Endothelial damage, autoregulation failure, and vessel wall thickening can lead to narrowing of lumen without complete occlusion.

Penetrating arteriole

 Decreased blood flow

Hyoperfused parenchyma

Appears normal on imaging

Complete occlusion

Severe stenosis

Third-order vessel

Second-order vessel

Large cerebral vessel

Blood-brain barrier degradation

Normal cerebral parenchyma

Lacunar stroke

White matter hyperintensity

Blood flow

Cerebral microinfarct
Etiology/Risk Factors

- Endothelial dysfunction & permeability increase exponentially with age.

- Hypertension & smoking are important treatable risk factors but 90% of disease seems unaccounted by conventional risk factors.

- High sodium intake > HBP; increased oxidative stress, vascular stiffness & impaired vasodilation.

- Likely genetics plays a large role.

- Low education, childhood poverty.

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### Table: Recent Genetic Studies of Lacunar Stroke and Cerebral Small Vessel Disease

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Type</th>
<th>Related Gene</th>
<th>Biomarker(s) Studied</th>
<th>SNP</th>
<th>Locus</th>
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<tbody>
<tr>
<td>Weng et al, 2012</td>
<td>Single gene</td>
<td>COL4A1</td>
<td>LS, ICH</td>
<td>rs515201</td>
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<td>Rannikmäe et al, 2017</td>
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<td>Lv et al, 2014</td>
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<td>Rannikmäe et al, 2017</td>
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<td>Rutten-Jacobs et al, 2016</td>
<td>Single gene</td>
<td>MTHFR</td>
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<td>Luo et al, 2017</td>
<td>Single gene</td>
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<td>Traylor et al, 2017</td>
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<td>Lopez et al, 2015</td>
<td>GWAS</td>
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</table>
SVD Treatments

- Control BP
- Stop smoking
- Exercise
- Avoid XS salt intake
- Dual antiplatelet therapy is harmful
SVD: New treatments?

- **Isosorbide mononitrate**
  - oxide donor
  - Potentially improves BBB integrity, vasodilation, reduces inflammation and neuroprotection

- **Cilostazol**
  - Phosphodiesterase 3 inhibitor
  - Improves BBB integrity, vasodilation, reduces vessel stiffness and inflammation

- LACI-2 (LACunar stroke Intervention) Phase 2 trial now ongoing
The commonest form of cerebrovascular disease is dementia, not stroke.

-Vladimir Hachinski
Vascular cognitive impairment is the second commonest cause of dementia.
It is present in at least 30% of demented patients.
Small vessel disease is the most important vascular contributor to dementia.
SVD and Cognition

Historically felt to affect frontal-subcortical networks with:

- Loss of mental processing speed
- Decreased executive function
- Slowed motor performance
- Impaired mood regulation
- Apathy and depression common
SVD and Cognition

Effects more diverse that previously recognized. Include deficits in:

- Language
- Memory
- Attention
- Visuospatial abilities

Remarkable heterogeneity in patients with radiologically similar degrees of SVD
Frank-Erik de Leeuw
Radboud University Medical Center
The Netherlands
a  Neuroimaging markers of SVD

- Brain atrophy
- WMH
- Lacune
- Microinfarcts

b  Heterogeneity, perilesional and remote effects of SVD

- Cortical thinning
- Lesion penumbra
- Lesion heterogeneity
- Microbleed
- Perivascular space
- White matter tract
- Coalescence of microinfarcts with resultant larger cortical infarct
Diffusion Tensor Imaging
Functional MRI
c  Structural and functional connectivity in SVD

Non-rich club  
Rich club  
Strategic infarct  
Rich-club connections

Impaired functional connectivity  
Increased network efficiency

d  Brain reserve and compensatory mechanisms in SVD

Larger total brain volume

Compensatory connectivity
Construction of brain networks

**c Structural and functional connectivity in SVD**
- Non-rich club
- Rich club
- Strategic infarct
- Rich-club connections
- ACC
- dIPFC
- Impaired functional connectivity
- Impaired structural connectivity

**d Brain reserve and compensatory mechanisms in SVD**
- ACC
- dIPFC
- Increased network efficiency
- Compensatory connectivity
- Larger total brain volume
SVD: Summary

• SVD accounts for
  • about 25% of strokes
  • at least 30% of dementia

• Endothelial failure > BBB permeability > vessel damage > tissue damage, demyelination, scarring, damage to connectome

• Lacunar infarcts are late events

• SVD pathology probably has an additive interaction with other degenerative diseases—especially Alzheimer’s
SVD Treatment

- Control BP
- Stop smoking
- Exercise
- Avoid XS salt intake
- Dual antiplatelet therapy is harmful
- Possibly isosorbide dinitrate and cilostasol
Thank you for your attention