Cerebral small vessel disease and Leukoaraiosis
What do we know?

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OUTLINE

• Small vessel disease

• Leukoariosis

• Cerebral amyloid angiopathy
What are small vessels?

Diameter < 300µm
artery

arteriole

capillary
Cerebral small vessel disease

• Not a single disease

• Group of diseases with different pathologies and different aetiologies

• affecting the small arteries, arterioles, venules and capillaries of the brain
Panel: Aetio-pathogenic classification of cerebral small vessel diseases

Type 1: arteriolosclerosis (or age-related and vascular risk-factor-related small vessel diseases)
- Fibrinoid necrosis
- Lipohyalinosis
- Microatheroma
- Microaneurysms (saccular, lipohyalinotic, asymmetric fusiform, bleeding globe)
- Segmental arterial disorganisation

Type 2: sporadic and hereditary cerebral amyloid angiopathy

Type 3: inherited or genetic small vessel diseases distinct from cerebral amyloid angiopathy
- For example, CADASIL, CARASIL, hereditary multi-infarct dementia of the Swedish type, MELAS, Fabry’s disease, hereditary cerebroretinal vasculopathy, hereditary endotheliopathy with retinopathy, nephropathy and stroke, small vessel diseases caused by COL4A1 mutations

Type 4: inflammatory and immunologically mediated small vessel diseases
- For example, Wegener’s granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schönlein purpura, cryoglobulinemic vasculitis, cutaneous leukocytoclasis angiitis, primary angiitis of the CNS, Sneddon’s syndrome, nervous system vasculitis secondary to infections, nervous system vasculitis associated with connective tissue disorders such as systemic lupus erythematosus, Sjögren’s syndrome, rheumatoid vasculitis, scleroderma, and dermatomyositis

Type 5: venous collagenosis

Type 6: other small vessel diseases
- For example, post-radiation angiopathy and non-amyloid microvessel degeneration in Alzheimer’s disease

CADASIL = cerebral autosomal dominant arteriopathy with subcortical ischaemic strokes and leukoencephalopathy.
CARASIL = cerebral autosomal recessive arteriopathy with subcortical ischaemic strokes and leukoencephalopathy.
MELAS = mitochondrial encephalopathy with lactic acidosis and stroke-like episodes.
• Not confined to the brain

• Systemic disorder

• Affect other organs – coronary arteries, kidneys, eyes etc
Coronal postmortem angiogram showing the branches of the anterior cerebral arteries
Vascular imaging
• In vivo small arteries cannot be visualized
Consequences of small vessel disease

• White matter lesions
• Lacunar infarcts
• Microbleeds
• Large haemorrhages
• Parenchymal lesions - marker of small vessel disease
• misleadingly small vessel disease is used to describe only the ischaemic component
  – Lacunar infarcts and white matter lesions

• risk of haemorrhage – should not be forgotten
Leukoariosis
What is it?

RADIOLOGICAL DIAGNOSIS
• Vascular
• Degenerative
  • Leukodystrophies
  • Inflammatory disorders
  • CADASIL etc

• Avoids assumptions about pathology
Importance

• Will see more and more

• Aging population

• More scans being done – reduced threshold for scanning
  – More scanners
  – More physicians and neurologists!
  – Patient expectations
Who

• **Stroke**
  – 7% of patients with ischaemic stroke had leukoariosis

• **Dementia**
  – Unselected dementia – 30-40 %
  – Vascular dementia – 60-70%
  – AD- 30%

• **Normal aging**
  – 10% - asymptomatic people 50-75
  – Prevalence increases with age
Pathology

- White matter
- Blood vessel abnormalities
White matter

- Major pathological findings are
  - myelin pallor
    - ? Dymelination
    - ? Loss of nerve fibres
  - enlargement of perivascular spaces
  - gliosis and axonal loss
Pathology of leukoaraiosis

H & E stain
Two small vessels (arrows) are shown with concentric hyaline thickening, loss of smooth muscle cells and with luminal narrowing. The perivascular space is widened, and the surrounding white matter appears gliotic.
Distribution

- Early - discrete
- Later - confluent and more widespread
Blood vessels

• Loss of smooth muscle cells from the tunica media
• Deposition of fibro-hyaline material - lipohyalinosis
• Thickening of the vessel wall
• Narrowing of the lumen

• Microatheroma formation
• Fibrinoid necrosis
• Some subdivide arteriosclerosis according to the most pronounced histological changes

• Lypohyalinosis
• Microatheroma
• Microaneurysm – Charcot bouchard

• Can coexist
lipohyalinosis
microaneurysm
microatheroma
fibrinoid necrosis
Cerebral small vessel disease subtypes?

- Leukoariosis
- Lacunar infarcts
<table>
<thead>
<tr>
<th>Leukoariosis</th>
<th>Lacunar infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Hypercholestrolaemia</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>(Homocysteine)</td>
</tr>
</tbody>
</table>
Mechanisms - leukoaraiosis

• Ischaemia?
• Blood-brain barrier dysfunction?
• Endothelial dysfunction?
• Leukoaraiosis and β amyloid?
Presentations

• stroke

• cognitive impairment

• gait disturbance and falls
Stroke
70 year old, sudden onset dysarthria
Cognitive impairment

1. slowing of the speed of information processing
2. executive dysfunction
• Mini-mental status examination is insensitive to executive dysfn and speed

• Letter fluency

• Trail making
Letter fluency

Say: ‘I’m going to give you a letter of the alphabet and I’d like you to generate as many words as you can beginning with that letter, but not names of people or places. Are you ready? You’ve got a minute and the letter is P’

Paper, pack, pin, popcorn, peel, pale, puzzle, pope, palace, puppy ..........
**Trail making test**

**Instructions:**
Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed both parts after five minutes have elapsed.
Trail making test
**Scoring:**
Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment.

<table>
<thead>
<tr>
<th>Trail</th>
<th>Average</th>
<th>Deficient</th>
<th>Rule of Thumb</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>29 seconds</td>
<td>&gt; 78 seconds</td>
<td>Most in 90 seconds</td>
</tr>
<tr>
<td>B</td>
<td>75 seconds</td>
<td>&gt; 273 seconds</td>
<td>Most in 3 minutes</td>
</tr>
</tbody>
</table>
Executive function screening

1. Observe pt- frontal lobe

2. Luria 3 step test (‘fist-edge-palm’ test)
   Complex task- checks premotor, prefrontal, parietal and visual memory

3. Grasp response

4. Imitation behaviour
Luria’s 3 step test (fist-edge-palm)
Grasp response
Imitation behaviour

- Clapping once
- Slapping each knee in turn
- Crossing your arms across your chest
Gait disorder and falls

• 80% - some degree of gait disorder

• Progression - deterioration of gait

• Link between gait disturbance and falls

• Falls - fractures and hospitalisation

• Recognition

• Assessment of gait/ fall risk / physiotherapy / home modifications
Typical gait

Slow, short stepped, **wide based,** shuffling gait

Lower body parkinsonism clinical picture
### Progression of leukoarriosis

<table>
<thead>
<tr>
<th></th>
<th>Initial stage</th>
<th>Intermediate stage</th>
<th>Terminal stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive performance</td>
<td>Mild deficits (e.g., in executive functions, attention, set-shifting abilities) appreciable only with appropriate cognitive tests</td>
<td>Clinically obvious cognitive deterioration not reaching the severity of dementia (corresponds to vascular subcortical mild cognitive impairment)</td>
<td>Dementia with associated memory deficits (i.e., subcortical vascular dementia)</td>
</tr>
<tr>
<td>Mood</td>
<td>Depressive symptoms</td>
<td>Depression</td>
<td>Not assessable</td>
</tr>
<tr>
<td>Sphincteric functions</td>
<td>From normal to urgency</td>
<td>Urinary incontinence episodes</td>
<td>Complete urinary incontinence, sometimes also faecal incontinence</td>
</tr>
<tr>
<td>Gait</td>
<td>From normal to mild slowing, subjective postural instability</td>
<td>Apraxic gait*</td>
<td>Bedridden</td>
</tr>
<tr>
<td>Pseudo-bulbar signs</td>
<td>Absent (primitive reflexes on neurological examination can be present)</td>
<td>Dysphagia, dysarthria, pathological laughing, and crying</td>
<td>Severe dysphagia (PEG might be required), unintelligible speech</td>
</tr>
</tbody>
</table>
Imaging

• MRI more sensitive

• Grade
  – Visual rating scales
Grade 1 (mild changes): single lesions <10 mm and/or areas of “grouped” lesions <20 mm in any diameter

Grade 2 (moderate changes): single hyperintense lesions 10-20 mm, and hyperintense areas linked by no more than “connecting bridges” >20 mm in any diameter

Grade 3 (severe changes): both single and confluent hyperintense areas of ≥20 mm in any diameter
Additional MRI sequences

• **DWI** – useful to differentiate new from old

• **Gradient echo** – previous haemorrhages or microbleeds

• **Diffusion tensor imaging**
  – better index of white matter damage – can be used to track disease progression
  – Normal appearing white matter

• **T1W Volumetrical assessment** - cerebral atrophy
Diffusion tensor imaging
colour-coded –
Hot colours (yellow to red to black) indicate increasing mean diffusivity (water diffusion averaged in all directions, which increases as tissue is damaged, removing the myelin and axonal membranes that restrict diffusion).

The variability of diffusion within areas of leukoaraiosis is evident.
Prognosis

• Increased risk of
  – ischaemic stroke
  – cerebral haemorrhage
  – vascular death
Effects of small vessel disease on age-related disability

LADIS (LeukoAriosis and DISability) study

- Multicentre
- >600 patients
- 65-84 years
- Independent in ADLs
- Base line – MRI + clinical assessment
- F/U – 3 years, final MRI + yearly clinical assessments
Kaplan-Meier probability of survival free of transition from independence in IADL to disability or death according to baseline severity grades in age related changes in white matter.
Therapeutic aspects

• Thrombolysis
• Carotid endarterectomy
• Anticoagulation
• Antiplatelet
• Cholesterol, blood pressure lowering
• Dementia
Thrombolysis

• Risk factors for haemorrhagic transformation
  • Age
  • Higher NIHSS score
  • BP/ Hyperglycaemia

• Leukoaraiosis

• CASES (Canadian Alteplase for Stroke Effectiveness Study)
  – Rate of sICH – 10% with moderate to severe leukoaraiosis as against average of 4.5%

• However leukoaraiosis is not a contraindication for thrombolysis

58
Carotid endartectomy

- NASCET – leukoraiosis on baseline CT – increased risk of peri-operative stroke and death

- Not contraindicated
Anticoagulation

- SPIRIT – stroke prevention in reversible ischaemia trial
- Warfarin vs aspirin in stroke patients in sinus rhythm
- Target INR 3-4.5; negative study

  - Age
  - Leukoariosis

- Predictors of major bleeding with anticoagulation
Cholestrol lowering

• SPARCL
• Stroke Prevention by Aggressive Reduction of Cholesterol Levels
• Atorvastatin - 80mg vs placebo
• Stroke/ TIA

• Small vessel disease and raised LDL similar benefit as large vessel disease group
Antiplatelets and antihypertensive

- **SPS3**
- **Secondary Prevention of Small Subcortical Strokes**
- Study specifically targeting small vessel disease

- 2 trials

- Trial 1
  - Double blind
  - Aspirin vs aspirin + clopidogrel

- Trial 2
- Open-arm – blood pressure control
  - Standard 130-149
  - Intensive < 130
Blood pressure control

• Can too intensive be detrimental
Dementia

- AChE inhibitors or NMDA antagonist (memantine) no clear benefit
- However significant proportion may have AD as well in which case it may be beneficial
Neuro-imaging as a surrogate of small vessel disease

- Antihypertensive
- Statin
- Antidiabetic

- Whether reduction of white matter burden leads to a decrease in incidence of cognitive and functional decline needs to be studied
Cerebral amyloid angiopathy (CAA)
Amyloid

- Insoluble extracellular fibrous protein - forms aggregates
- sharing specific structure – β sheet
β sheet (β-pleated sheet)
<table>
<thead>
<tr>
<th>Disease</th>
<th>Protein featured</th>
<th>Official abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Beta amyloid</td>
<td>Aβ</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>IAPP (Amylin)</td>
<td>AIAPP</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>Alpha-synuclein</td>
<td>none</td>
</tr>
<tr>
<td>Transmissible spongiform encephalopathy</td>
<td>PrP&lt;sup&gt;Sc&lt;/sup&gt;</td>
<td>APrP</td>
</tr>
<tr>
<td>Huntington's Disease</td>
<td>Huntingtin</td>
<td>none</td>
</tr>
<tr>
<td>Medullary carcinoma of the thyroid</td>
<td>Calcitonin</td>
<td>ACal</td>
</tr>
<tr>
<td>Cardiac arrhythmias, Isolated atrial amyloidosis</td>
<td>Atrial natriuretic factor</td>
<td>AANF</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Apolipoprotein AI</td>
<td>AApoA1</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Serum amyloid A</td>
<td>AA</td>
</tr>
<tr>
<td>Prolactinomas</td>
<td>Prolactin</td>
<td>APro</td>
</tr>
<tr>
<td>Familial amyloid polyneuropathy</td>
<td>Transthyretin</td>
<td>ATTR</td>
</tr>
<tr>
<td>Hereditary non-neuropathic systemic amyloidosis</td>
<td>Lysozyme</td>
<td>ALys</td>
</tr>
<tr>
<td>Dialysis related amyloidosis</td>
<td>Beta 2 microglobulin</td>
<td>Aβ2M</td>
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<tr>
<td>Finnish amyloidosis</td>
<td>Gelsolin</td>
<td>AGel</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy</td>
<td>Beta amyloid</td>
<td>Aβ</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy (Icelandic type)</td>
<td>Cystatin</td>
<td>ACys</td>
</tr>
<tr>
<td>systemic AL amyloidosis</td>
<td>Immunoglobulin light chain AL</td>
<td>AL</td>
</tr>
</tbody>
</table>
CAA

• ~ 30% of asymptomatic elderly people

• Characterized by
  – Deposits of homogeneous eosinophilic material
  – in the media and adventitia of arterioles and small arteries of the cortex and leptomeninges
H & E stain
deposits of amyloid (acellular eosinophilic material) within the vessel wall

Staining with Congo red
amyloid - within the vessel wall exhibits apple-green birefringence under polarized light
CAA

• Definite CAA - histopathological analysis
  • Autopsy
  • In vivo- Brain biopsy (cortical and leptomeningeal)

• Probable CAA - Imaging

• Genetic analysis
71-year-old man with probable CAA
• Gradient-echo MRI

• Haemosiderin deposits - which suggest microhaemorrhages

• Although healthy people can have signs of previous cerebral microhaemorrhages, cortical and corticosubcortical lesions suggest CAA

• Detection of new small haemorrhages on T2*-gradient echo-weighted MRI at follow-up are potential markers of advanced vascular pathology and disease progression
### ICH

<table>
<thead>
<tr>
<th>Hypertension related</th>
<th>CAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors</td>
<td>Hypertensive</td>
</tr>
<tr>
<td>Age</td>
<td>Younger, Older &gt; 70</td>
</tr>
<tr>
<td>Location</td>
<td>..... Lobar – occipital / parietal</td>
</tr>
<tr>
<td>Annual risk of recurrence</td>
<td>2%, 10.5%</td>
</tr>
<tr>
<td>Size of affected vessel</td>
<td>Small arteries, Small and medium</td>
</tr>
</tbody>
</table>
Take home messages ...

- Do not overlook a radiological diagnosis of small vessel disease
- Ask yourself which type of small vessel disease
- Cognitive deficits – MMSE may miss
- Assess fall risk
- Do not withhold thrombolysis and carotid endarterectomy in this group, inform higher risk involved
- Warfarin – increased risk of ICH and gait disorder - fall risk has to be taken into account