Neuropathology of Neurodegenerative Disorders
Prof. Jillian Kril

Neurodegenerative disorders to be discussed
• Alzheimer’s disease
• Lewy body diseases
• Frontotemporal dementia and other tauopathies
• Huntington’s disease
• Motor Neuron Disease

Neuropathology of neurodegeneration
• Macroscopic features of disease
• Extent and severity of atrophy
• Microscopic features
• Diagnostic criteria
Neuropathology of Ageing

• Cohort effect
• Atrophy
  – White matter only
  – ~2mL/y
• Neuron loss
  – No loss from hippocampus, entorhinal and superior temporal cortices
• Accumulation of plaques and tangles

Age-associated accumulation of plaques and tangles

Data from Ref 2

Age-associated accumulation of plaques and tangles

Data from Ref 2

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Neurodegenerative disorders

- Alzheimer's disease
- Lewy body diseases
- Frontotemporal dementia and other tauopathies
- Huntington's disease
- Motor Neuron Disease

AD: Macroscopic pathology

AD: Macroscopic pathology
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Determination of Regional Volumes

Cortical surfaces painted
3mm coronal slices
Volumes determined by point count technique

Volume loss = Neuron loss

Regional atrophy in AD

Data from Ref 4

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**AD: Neuropathological Diagnosis**

- Neurofibrillary tangles
- Ab plaques

**AD: Plaques**

- Diffuse
- Neuritic
- Compact

*Ab Courtesy C Shepherd*

**CERAD criteria**

Age-associated accumulation of plaques

- Sparse
- Moderate
- Frequent

- <50y
- 50-75y
- >75y

- AD
- possible AD
- not AD
- possible AD
- probable AD
- AD
- possible AD
- probable AD
- AD

Ref 5

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**AD: Neurofibrillary tangles**
Progression of NFTs

- Pre-tangle
- Early
- Mature
- Ghost

**AD: Neurofibrillary tangles**
Spread of NFTs

- Transentorhinal
- Entorhinal
- CA1
- Neocortex

**Braak staging of NFTs**
Region-specific accumulation of NFTs

<table>
<thead>
<tr>
<th>Braak Staging</th>
<th>Entorhinal</th>
<th>CA1</th>
<th>Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not AD</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>I</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>II</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Possible AD</td>
<td>III</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>IV</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>AD</td>
<td>V</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>VI</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

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NIA-Reagan Institute Criteria

<table>
<thead>
<tr>
<th>Probability</th>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaques</td>
<td>Frequent</td>
<td>Moderate</td>
<td>Infrequent</td>
</tr>
<tr>
<td>NFTs</td>
<td>Cortical</td>
<td>Limbic</td>
<td>Few</td>
</tr>
<tr>
<td>B&amp;B stage</td>
<td>V-VI</td>
<td>III-IV</td>
<td>I-II</td>
</tr>
</tbody>
</table>

Nucleus Basalis of Meynert (NbM)

- 40-80% cell loss
- Relates to dementia severity
- Relates to cortical atrophy
- Lost due to NFTs

Neuron loss in AD

- Entorhinal cortex: 48% early
- Hippocampal CA1: 69%
- Superior temporal cortex: >50%
- Locus coeruleus: ~65%
- Raphe nuclei: 25-70%
- Nucleus Basalis of Meynert: 56%
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Neuron loss in AD

• Entorhinal cortex ?
• Hippocampal CA1 no
• Superior temporal cortex no
• Locus coeruleus ?
• Raphe nuclei no
• Nucleus Basalis of Meynert yes

Due to NFT formation

Neurodegenerative disorders

• Alzheimer’s disease
• Lewy body diseases
• Frontotemporal dementia and other tauopathies
• Huntington’s disease
• Motor Neuron Disease

Lewy body diseases

PD Normal α-synuclein

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LBD: Neuropathological diagnosis

- Brainstem Lewy bodies (=PD)
- Limbic
  - Frequent (5+) in cingulate
  - Present in parahippocampus
- Neocortical
  - Limbic LBs
  - Frequent (5+)
in temporal neocortex

Spread of Lewy bodies
Braak Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>I &amp; II</td>
<td>Medulla, Olfactory</td>
</tr>
<tr>
<td>III &amp; IV</td>
<td>Midbrain, Pons, NbM</td>
</tr>
<tr>
<td>V &amp; VI</td>
<td>Neocortices</td>
</tr>
</tbody>
</table>

Spread of Lewy bodies
Braak Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>V &amp; VI</td>
<td>Neocortices</td>
</tr>
</tbody>
</table>

Ref 8
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Regional atrophy in DLB

DLB: Other Pathology

Neurodegenerative disorders
- Alzheimer's disease
- Lewy body diseases
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- Motor Neuron Disease

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FTLD: Macroscopic pathology

FTLD: Macroscopic pathology

Regional atrophy in FTLD

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FTLD: Disease staging

<table>
<thead>
<tr>
<th>Control</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>E</td>
</tr>
</tbody>
</table>

Ref 10

Tauopathy: Distribution by stage

<table>
<thead>
<tr>
<th>Tau +ve</th>
<th>Tau −ve</th>
<th>CBD #</th>
<th>PSP #</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT D*</td>
<td>FT D*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N 11 13 9 24

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (23%)</td>
<td>3 (11%)</td>
<td>1 (62%)</td>
<td></td>
</tr>
<tr>
<td>2 (18%)</td>
<td>5 (38%)</td>
<td>4 (44%)</td>
<td>7 (29%)</td>
</tr>
<tr>
<td>6 (55%)</td>
<td>3 (23%)</td>
<td>4 (44%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>3 (27%)</td>
<td>2 (15%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Ref 10; # Ref 11

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FTLD: Neuropathological diagnosis

- **Tau-positive**
  1. Intraneuronal - Pick's Disease
  2. Extraneural - CBD, PSP

- **Tau-negative**
  3. Ubiquitin-positive, tau-negative inclusions (FTLD-U or FTLD+MND)
  4. Absence of inclusions (DLDH)

Ref 12

FTLD: Neuron loss

<table>
<thead>
<tr>
<th></th>
<th>Early (Stages 1 &amp; 2)</th>
<th>Late (Stages 3 &amp; 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal cortex - layer III</td>
<td>77%</td>
<td>58%</td>
</tr>
<tr>
<td>Frontal cortex - layer V</td>
<td>81%*</td>
<td>60%*</td>
</tr>
<tr>
<td>Temporal cortex - layer III</td>
<td>63%</td>
<td>48%</td>
</tr>
<tr>
<td>Temporal cortex - layer V</td>
<td>76%</td>
<td>56%</td>
</tr>
<tr>
<td>CA1 of hippocampus</td>
<td>81%</td>
<td>24%</td>
</tr>
<tr>
<td>Astrocyte density</td>
<td>377%*</td>
<td>458%*</td>
</tr>
</tbody>
</table>

Significantly different from *control and #early values
Ref 13

Neurodegenerative disorders

- Alzheimer's disease
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- Motor Neuron Disease

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**Huntington’s disease**

- Autosomal dominant
- CAG-repeats in HD gene on chromosome 4 (others = SCA, DRPLA, Kennedy’s disease)
- Age of onset related to number of repeats

<table>
<thead>
<tr>
<th>No. repeats</th>
<th>Age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>8-39</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>40-50</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
</tr>
</tbody>
</table>

Data from Ref 14

**Regional atrophy in HD**

**HD: Macroscopic pathology**
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### HD: Disease staging
- Caudate
- Putamen
- Accumbens

Stage 1
Stage 2
Stage 3
Stage 4

Ref. 15

### HD: Microscopic pathology
**Striatum**
- Loss of medium spiny neurons
- Astrocytosis
  - Severity related to stage
- Intranuclear inclusions of mutant protein

**Other**
- Neocortex
- Entorhinal cortex
- Nucleus basalis
- Amygdala
- Severity related to stage

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Neurodegenerative disorders

- Alzheimer’s disease
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- Motor Neuron Disease

Motor Neuron Disease

- Complex of disorders
- Motor neuron loss
- Inherited forms
  - SOD1 (~20%)
- Juvenile forms

Motor Neuron Diseases

<table>
<thead>
<tr>
<th></th>
<th>Upper MN</th>
<th>Brain stem MN</th>
<th>Lower MN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>PMA</td>
<td>✓ (Late &gt;50%)</td>
<td>✓ (Late ~85%)</td>
<td>✓</td>
</tr>
<tr>
<td>PLS</td>
<td>✓</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>
ALS: Microscopic pathology

Conclusions

- Brain atrophy
  - Anatomical distribution
  - Severity of atrophy
- Atrophy reflects neuron loss
- Unique microscopic features
- Overlapping microscopic features
- Evolving neuropathological criteria
References

Acknowledgements
Thank you to Glenda Halliday and Heidi Cartwright for the use of artwork and artwork in this presentation.

The author's research is supported by the National Health and Medical Research Council of Australia.

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