Neuropathology of old-age dementia

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Dementia types

Alzheimer’s dementia

- Dementia with Lewy Bodies
- Frontotemporal dementia
- Dementia in Parkinson’s Disease

Vascular Dementia

Mixed Alzheimer’s and Vascular Dementia

Other?
Dementia prevalence

Based on percentage of the 80+ population

Estimated increase in percentage of the 80+ population

CFAS I, England and Wales, 1989-1993
United Nations, Department of Economic and Social Affairs, Population Division (2011)
Challenges of dementia diagnosis in the older old

- Cognitive decline viewed as “normal aging”
- Comorbidities, medications
- Lack of normative neuropsychological data
- Limitations of standard diagnostic criteria
Dementia in the oldest old

Alzheimer’s dementia

Vascular Dementia

Other?

Mixed Alzheimer’s and Vascular Dementia
Nueuropathology of dementia

Bias in pathological studies
MRC Cognitive Function and Ageing Study (CFAS)

- start in 1989
- 65+ year olds
- Oxford, Ely, Nottingham, Gwynedd, Liverpool, Newcastle
MRC Cognitive Function and Ageing Study (CFAS)

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n= 18226
MRC Cognitive Function and Ageing Study (CFAS)

- start in 1989
- 65+ year olds
- Oxford, Ely, Nottingham, Gwynedd, Liverpool, Newcastle
- interviews
- cognitive examinations

n= 18226 follow-up
- start in 1989
- 65+ year olds
- Oxford, Ely, Nottingham, Gwynedd, Liverpool, Newcastle

n= 18226 follow-up

†
n= 565

- interviews
- cognitive examinations

- fixed / frozen
- CERAD protocol

MRC Cognitive Function and Ageing Study (CFAS)
Neuropathological Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prevalence of diagnosis (%)</th>
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<tbody>
<tr>
<td>Normal brain</td>
<td>5</td>
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<tr>
<td>Insufficient plaques and tangles</td>
<td>38</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>38</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>3</td>
</tr>
<tr>
<td>Cortical Lewy bodies</td>
<td>3</td>
</tr>
<tr>
<td>Insufficient cortical Lewy bodies</td>
<td>4</td>
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<tr>
<td>Vascular disease</td>
<td>52</td>
</tr>
<tr>
<td>Others</td>
<td>12</td>
</tr>
</tbody>
</table>

MRC CFAS. Lancet 2001
Neuropathological Diagnosis

Prevalence of diagnosis (%)

- Normal brain: 13% Dementia, 87% No dementia
- Insufficient plaques and tangles: 38% Dementia, 62% No dementia
- Alzheimer's disease: 82% Dementia, 18% No dementia
- Parkinson's disease: 87% Dementia, 13% No dementia
- Cortical Lewy bodies: 83% Dementia, 17% No dementia
- Insufficient cortical Lewy bodies: 72% Dementia, 28% No dementia
- Vascular disease: 58% Dementia, 42% No dementia
- Others: 64% Dementia, 36% No dementia

MRC CFAS. Lancet 2001
Neocortical AD pathology and age

- **Atrophy**
  - With dementia
  - Without dementia

- **Neuritic Plaques**
  - With dementia
  - Without dementia

- **Tangles**
  - With dementia
  - Without dementia
Case report

**age:** 75 – 80 – 85 – 90 – 95 – 100 – 102

**MMSE:** 29 – 28 – 28 – 25 – 21 – 14

**medication:** antihypertensiva donepezil memantine

**IADL**  **ADL**
Case report

AD type pathology **expected** in autopsy

- Neuritic plaques
- Neurofibrillary tangles
- Neuropil threads

CERAD score

Braak stage

www.translationalscience.msu.edu 12/2014
Pathological examination:

- CERAD neuritic plaque score: 0
- Braak stage for neurofibrillary tangles: II
- No significant vascular pathology
Case report

Pathological examination:
Old-age hippocampal sclerosis is a cause of dementia

- Normal CA1
- Hippocampal sclerosis (HScl)
### Characteristics of HScI

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology</td>
<td>Genetics</td>
</tr>
</tbody>
</table>
Characteristics of HScI

- Alzheimer's type: 46%
- Alzheimer's type and vascular: 27%
- Vascular: 9%
- Depressive illness: 9%
- No dementia: 9%

Prevalence

Pathology

Genetics
Characteristics of HScl

- Alzheimer's type: 46%
- Alzheimer's type and vascular: 27%
- Vascular: 9%
- Depressive illness: 9%
- No dementia: 9%

Pathology

Genetics

Graph showing prevalence over age at death for Braak stage V-VI and HScl.
Characteristics of HScI

- 46% Alzheimer’s type
- 27% Alzheimer’s type and vascular
- 9% Vascular
- 9% Depressive illness
- 9% No dementia

Prevalence of TDP-43

- Dentate: 22% HScI, 2% no HScI
- CA4: 67% HScI, 2% no HScI
- CA3/2: 78% HScI, 8% no HScI
- CA1: 88% HScI, 25% no HScI

Braak stage V-VI prevalence:
- ≤89: 0%
- 90-99: 10%
- ≥100: 40%

Genetics

** p<0.001
Characteristics of HScl

Prevalence of TDP-43

<table>
<thead>
<tr>
<th>GRN rs5848</th>
<th>genotype, n</th>
<th>non-HScl</th>
<th>HScl</th>
<th>statistic</th>
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<tbody>
<tr>
<td></td>
<td>CC</td>
<td>214</td>
<td>8</td>
<td>$\chi^2 = 8.30$</td>
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<tr>
<td></td>
<td>CT</td>
<td>157</td>
<td>9</td>
<td>$p = 0.016$</td>
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<tr>
<td></td>
<td>TT</td>
<td>35</td>
<td>6</td>
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Allelic frequency

<table>
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<tr>
<th></th>
<th>C</th>
<th>T</th>
<th>$\chi^2$</th>
<th>$p$</th>
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</thead>
<tbody>
<tr>
<td>Dentate</td>
<td>0.72</td>
<td>0.28</td>
<td>6.20</td>
<td>0.013</td>
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<tr>
<td>CA4</td>
<td>0.67</td>
<td>0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA3/2</td>
<td>0.78</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA1</td>
<td>0.88</td>
<td>0.12</td>
<td></td>
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</tr>
</tbody>
</table>

% of cases

- HScI
- no HScI

** $p<0.001$
• With increasing age, dissociation of clinical and pathological findings
• With increasing age, more mixed pathology
• Population-based clinicopathological studies are an invaluable research resource
• HScl presents clinically similar to AD, but associates pathologically with TDP-43
Thank you!

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