Neuropathology of dementias

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DISCLOSURES

• Sponsored research agreement with Biogen (to perform autopsies on subject from clinical trials)
Learning objectives

• Understand how neuropathologists render diagnoses

• Know how to read an autopsy report and interpret it for a family

• Appreciate clinico-neuropathological correlations associated with dementia
Diseases to be discussed

• Alzheimer disease

• Lewy body diseases

• Frontotemporal lobar degenerations

• Cerebrovascular diseases
Critical concept

- Neurodegenerative diseases are progressive disorders (from normal cognition to dementia)
- Pathologic lesions can be seen in advance of clinical end-point
- Therefore, can find lesions in subjects who are normal/mildly impaired

* disease $\neq$ dementia
Alzheimer disease

• Plaques
  – Extracellular deposits of Aβ (40-42 amino acid peptide cleaved from a larger protein)
  – **Genetic evidence links Aβ to AD**
Assessment of amyloid

• Where is it?
  – Distribution across anatomic structures
  – Thal scoring of amyloid

• What does it do to the surrounding brain?
  – Presence of neuritic plaques (abnormal neuronal processes around the amyloid deposit)
  – CERAD scoring of neuritic plaques
Thal scoring of amyloid

- **Distribution** of parenchymal deposits

- **Stages:**
  1 – Neocortical
  2 – Allocortex (hippocampus)
  3 – Thalamus, striatum, NbM
  4 – Brainstem
  5 – Cerebellum

[Thal et al. Neurology. 2002; 58(12):1791-800]
Assessment of amyloid

- Where is it?
  - Distribution across anatomic structures
  - Thal scoring of amyloid
- What does it do to the surrounding brain?
  - Presence of neuritic plaques (abnormal neuronal processes around the amyloid deposit)
  - CERAD scoring of neuritic plaques
Silver stain
AD: CERAD

- Neuritic plaques
- Frontal, temporal and parietal cortex
- Assess on WORST area
- Reporting:
  - Absent
  - Sparse
  - Moderate
  - Frequent
Alzheimer disease

• Plaques
  – Extracellular deposits of Aβ (40-42 amino acid peptide cleaved from a larger protein)
  – **Genetic evidence links Aβ to AD**

• Tangles
  – Deposits of hyperphosphorylated tau (microtubule binding protein)
  – **Genetic evidence links tau to FTLD**
AD: Braak & Braak

• Developed as a staging scheme

• Assumption: lesion develop in a stereotyped order across anatomic sites

AD: Braak & Braak

• Stages I-II: “transentorhinal” disease
  – No cases had clinical diagnosis of dementia

• Stages III-IV: “limbic” disease
  – 5 of 10 Stage III cases and 5 of 10 Stage IV cases had clinical diagnosis of dementia

• Stages V-VI: “isocortical” disease
  – All cases had clinical diagnosis of dementia
2012 NIA-Alzheimer Association

DOI 10.1007/s00401-011-0910-3

CONSENSUS PAPER

National Institute on Aging–Alzheimer’s Association guidelines for the neuropathologic assessment of Alzheimer’s disease: a practical approach

Thomas J. Montine · Creighton H. Phelps · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Charles Duyckaerts · Matthew P. Frosch · Eliezer Masliah · Suzanne S. Mirra · Peter T. Nelson · Julie A. Schneider · Dietmar Rudolf Thal · John Q. Trojanowski · Harry V. Vinters · Bradley T. Hyman

Alzheimer’s & Dementia 8 (2012) 1–13

Featured Articles

National Institute on Aging–Alzheimer’s Association guidelines for the neuropathologic assessment of Alzheimer’s disease

2012 NIA-Alzheimer Association

- Any plaques (± tangles) implies “Alzheimer disease neuropathologic changes” [ADNC]
- Report an “ABC” score
  - A is for Amyloid (Thal)
  - B is for Braak
  - C is for CERAD
- Use population-based observations to suggest likelihood of cognitive impairment
<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Based on Thal staging</td>
<td>Based on Braak staging</td>
<td>Based on CERAD score</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
</tr>
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<td>1</td>
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<td>1 - - - - I or II</td>
<td>- - - - None</td>
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<tr>
<td>2</td>
<td>- - - - - 3</td>
<td>2 - - - - III or IV</td>
<td>1 - - - - Sparse</td>
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<tr>
<td>3</td>
<td>- - - - 4 or 5</td>
<td>3 - - - - V or VI</td>
<td>2 - - - Moderate</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>3 - - - - Frequent</td>
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### 2012 NIA-Alzheimer Association

<table>
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<th>AD Neuropathologic Change</th>
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<td>C</td>
<td>0 or 1</td>
<td>2</td>
<td>3</td>
</tr>
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<tr>
<td></td>
<td>1</td>
<td>0 or 1</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
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<td>2 or 3</td>
<td>Low</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Intermediate</td>
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<td>Low</td>
<td>Intermediate</td>
<td>Intermediate</td>
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<td>0 or 1</td>
<td>Low</td>
<td>Intermediate</td>
<td>Intermediate</td>
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<tr>
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<td>2 or 3</td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
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</table>
Alzheimer disease reporting

- Alzheimer disease neuropathologic changes [ADNC]
  - Thal score for amyloid
  - Braak & Braak stage of tangles
  - CERAD score for neuritic plaques
  - ABC score, with interpretation of likelihood of cognitive impairment
Dementia with Lewy Bodies (DLB)

• Pathologic features:
  – Lewy bodies (absolute requirement)
  – Lewy neurites
  – Appropriate neuronal loss in brain stem (SN, LC)
  – Spongiform changes, especially in upper layers of entorhinal cortex [common not required]
Braak staging of LB pathology

Presymptomatic phase

Symptomatic phase

Threshold

1. Medulla
2. Pons
3. Midbrain
4. Limbic ctx
5. Assn. ctx
6. Primary ctx

Neocortex, primary, secondary
Neocortex, high order association
Mesocortex, thalamus
Substantia nigra, amygdala
Gain setting nuclei
Dorsal motor X nucleus
Stages of the PD-related path. process

Parkinson’s disease-related alterations

Advancing Diagnosis and Discovery
Dementia with Lewy Bodies (DLB)  
Newcastle criteria

<table>
<thead>
<tr>
<th>Score</th>
<th>LB per gyrus</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1-5</td>
</tr>
<tr>
<td>2</td>
<td>&gt;5</td>
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<table>
<thead>
<tr>
<th></th>
<th>Ent</th>
<th>Cin</th>
<th>Tem</th>
<th>Fr</th>
<th>Pa</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Brainstem</td>
<td>0-1</td>
<td>0-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0-2</td>
</tr>
<tr>
<td>Limbic</td>
<td>1-2</td>
<td>1-2</td>
<td>0-1</td>
<td>0-1</td>
<td>0</td>
<td>3-6</td>
</tr>
<tr>
<td>Neocortical</td>
<td>2</td>
<td>2</td>
<td>1-2</td>
<td>1-2</td>
<td>1-2</td>
<td>7-10</td>
</tr>
</tbody>
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# 2012 NIA-Alzheimer Association Reporting LB changes

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>No LBs or related changes in IHC for $\alpha$-synuclein</td>
</tr>
<tr>
<td>Brainstem-predominant</td>
<td>LBs in medulla, pons, or midbrain</td>
</tr>
<tr>
<td>Limbic (Transitional)</td>
<td>LBs in cingulate or entorhinal cortices, usually with brainstem involvement</td>
</tr>
<tr>
<td>Neocortical (Diffuse)</td>
<td>LBs in frontal, temporal, or parietal cortices usually with involvement of brainstem and limbic sites, which may include amygdala</td>
</tr>
<tr>
<td>Amygdala-predominant</td>
<td>LBs in amygdala with paucity of LBs in the above regions</td>
</tr>
</tbody>
</table>
Frontotemporal lobar degenerations (FTLD)

• Degenerations not dementias
• Basis for classification:
  – Distribution of lobar atrophy
  – Type of inclusions
  – Pattern of clinical symptoms
• bvFTD vs PPA (including subtypes)
FTLD

• Severe cortical neuronal loss and gliosis (basis for gross atrophy)

• Microscopic changes mirror the grossly evident atrophy

But…

• Microscopic changes commonly exceed the gross changes
FTLD -- inclusions

• Basis for neuropathologic classification
• Least specific marker: ubiquitin
• Two dominant more specific markers:
  – Tau
  – TDP-43
FTLD-tau

- Mutations in MAPT gene for tau (chromosome 17) are causative – BUT many cases are sporadic
- Mutations can be coding region or change in splicing
- Most inclusions are mixtures of 3R & 4R tau, except for Pick bodies (just 3R tau)
FTLD-tau
FTLD-tau/Pick Disease
FTLD-TDP (TDP-43)

- RNA-binding protein (many RNA targets)
- Normal: Nuclear localization
- Disease: Aggregates and relocates to cytoplasm (Neuronal cytoplasmic inclusions); intra-nuclear aggregates (Neuronal intra-nuclear inclusions)
- Aggregates can also occur in neurites (dystrophic neurites)
FTLD-TDP
TDP-43 associated diseases

• Sporadic and genetic FTLD-TDP exist
  – TDP-43 gene
  – C9orf72
  – Progranulin
  – Valosin-Containing Protein (VCP)

• Relationship with ALS:
  – Clinical and familial (C9orf72>>TDP-43)
  – Shared patterns of inclusions (distinct from ALS with SOD1 mutations)
## Patterns of FTLD-TPD

<table>
<thead>
<tr>
<th>Type</th>
<th>Inclusions</th>
<th>Phenotype</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Many NCI</td>
<td>bvFTD</td>
<td>GRN mutations</td>
</tr>
<tr>
<td></td>
<td>Short DN</td>
<td>PNFA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Layer 2 burden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Some NCI</td>
<td>bvFTD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rare DN</td>
<td>FTD with MND</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All layers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Rare NCI</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Many long DN</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Layer 2 burden</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NCI: Neuronal cytoplasmic inclusions; DN: dystrophic neurites; NII: Neuronal intra-nuclear inclusions
FTLD Reporting

• If tau containing inclusions:
  – FTLD-tau
    • Pick disease (3R tau, round inclusions)
  – Specify mutation status, if known (MAPT)
FTLD Reporting

• If TDP-43 containing inclusions:
  
  – FTLD-TDP
    
    • Specify subtype
    • Specify mutation status, if known
      – TDP-43
      – Progranulin
      – C9ORF72 hexanucleotide repeat expansion
FTLD Reporting

- If ubiquitin-positive, tau-negative, TDP-43-negative containing inclusions:
  - FTLD-other
  - Specify mutation status, if known
    - Range of rarer loci
Cerebrovascular disease

• Large vessel diseases
  – Atherosclerosis
  – “Strategic” infarction

• Small vessel diseases
  – Arteriolar sclerosis (hypertension)
  – Leukoariosis (white matter changes)
  – Microinfarcts
  – Cerebral amyloid angiopathy
Clinicopathologic correlation

• Presence of one neuropathologic disease is not ‘protective’ for other diseases

• Dementia is commonly associated with evidence of multiple neuropathologic processes

• Impossible to assign “blame”
Interaction of infarct and AD

Snowdon, et al. (1997) JAMA 277:813-817

Table 2.—Prevalence of Dementia for Participants Without and Participants With Brain Infarcts Who Met Neuropathologic Criteria for Alzheimer Disease*

<table>
<thead>
<tr>
<th>Type and Location of Infarct</th>
<th>Proportion Demented (No. Demented/No. at Risk)</th>
<th>Multivariate-Adjusted Odds Ratio for Dementia (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 Lacunar infarcts in basal ganglia, thalamus, or deep white matter</td>
<td>0.93 (14/15)</td>
<td>20.7 (1.5-288.0)</td>
</tr>
<tr>
<td>≥1 Large infarcts in lobes of neocortex</td>
<td>0.75 (9/12)</td>
<td>6.7 (0.9-48.3)</td>
</tr>
<tr>
<td>No brain infarcts</td>
<td>0.57 (21/37)</td>
<td>...</td>
</tr>
</tbody>
</table>
## Impact of microinfarcts

<table>
<thead>
<tr>
<th>Cognitive Outcome</th>
<th>Estimate (SE), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognition</td>
<td>$-0.287 (0.113), 0.012$</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>$-0.279 (0.138), 0.044$</td>
</tr>
<tr>
<td>Semantic memory</td>
<td>$-0.391 (0.130), 0.003$</td>
</tr>
<tr>
<td>Working memory</td>
<td>$-0.146 (0.099), 0.139$</td>
</tr>
<tr>
<td>Perceptual speed</td>
<td>$-0.400 (0.117), &lt;0.001$</td>
</tr>
<tr>
<td>Visuospatial abilities</td>
<td>$-0.153 (0.098), 0.119$</td>
</tr>
</tbody>
</table>


Adjusted for age-at-death, sex, education, large infarcts, AD and LB
1242 cases with neuropathologically diagnosed AD

AD; 43.7%
AD+VaD; 27.4%
AD+LBD; 16.7%
AD+LBD+VaD; 7.2%
Other; 5.1%
AD+tau; 1.7%
AD+HS; 0.5%
AD+VaD+tau; 0.7%
AD+VaD+HS; 0.6%
AD+LBD+tau; 0.6%
AD+LBD+HS; 0.2%
AD+LBD+VaD+HS; 0.5%
AD+LBD+VaD+tau; 0.2%

[Courtesy of Dennis Dickson, Mayo Clinic Jacksonville]
Diseases to be discussed

• Alzheimer disease

• Lewy body diseases

• Frontotemporal lobar degenerations

• Cerebrovascular diseases