Alzheimer’s Disease and Common Co-Morbidities

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Associate Director, Penn Alzheimer’s Disease Research Center
Associate Professor, Department of Pathology & Laboratory Medicine
Session Learning Objectives

• Determine the distribution and severity of Alzheimer’s disease neuropathologic change

• Name the major co-morbid neuropathologic changes that are associated with dementia

• Describe how to coalesce neuropathologic and other data into a comprehensive autopsy report
**Neurodegenerative Disease Overview**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Lesions</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease</td>
<td>Senile plaques, Neurofibrillary tangles</td>
<td>Amyloid β, Tau</td>
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<tr>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Cytoplasmic inclusions</td>
<td>TDP-43</td>
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<td>Parkinson’s Disease</td>
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<td>Dementia with Lewy Bodies</td>
<td>Lewy bodies</td>
<td>α-synuclein</td>
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<td>Tauopathies (i.e. Pick’s Disease, Progressive Supranuclear Palsy)</td>
<td>Neuronal and glial inclusions</td>
<td>Tau</td>
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<tr>
<td>Frontotemporal Degeneration</td>
<td>Cytoplasmic and nuclear inclusions</td>
<td>TDP-43/Tau</td>
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<td>Multiple System Atrophy</td>
<td>Glial cytoplasmic inclusions</td>
<td>α-synuclein</td>
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<td>Prion Disease</td>
<td>Spongiform degeneration, Prion plaques</td>
<td>Prion protein</td>
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<td>Trinucleotide Repeat Diseases (i.e. Huntington’s Disease)</td>
<td>Nuclear and cytoplasmic inclusions</td>
<td>Polyglutamine expansion</td>
</tr>
<tr>
<td>Chronic Traumatic Encephalopathy</td>
<td>Neuronal and glial inclusions</td>
<td>Tau</td>
</tr>
</tbody>
</table>
Part I: Alzheimer’s Disease Neuropathologic Change (ADNC)
Dementia

Progressive and irreversible syndrome characterized by cognitive dysfunction typically over multiple cognitive domains resulting in impairment in activities of daily living.
Dementia

Progressive memory dysfunction

Stepwise neurologic decline

Behavioral/Personality changes

Language dysfunction

Movement disorder

Weakness, spasticity
Dementia

Progressive memory dysfunction

Stepwise neurologic decline

Cerebrovascular disease

Amyloid plaques
Neurofibrillary tangles

Behavioral/Personality changes

Language dysfunction

TDP-43
Tau

TDP-43
Weakness, spasticity

Movement disorder

Lewy Bodies
Alzheimer’s Disease

• Auguste Deter

• Severe memory deficits
• Cognitive impairments
• Speech difficulties
• Perceptual abnormalities including hallucinations and delusions

• Died on April 8, 1906 (51 years old) due to complications from a decubitus ulcer
Genetics of Alzheimer’s Disease

Familial Cases

Early Onset (<10%)
- Chr1 PS2
  - 20%
- Chr14 PS1
  - 75%
- Chr21 APP
  - <5%
- Other

Late Onset (>90%)
- Chr19 APOE
- Chr6 TREM2
- Others
Genetic meta-analysis of diagnosed Alzheimer’s disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing
Alzheimer’s Disease, Gross Pathology
Diffuse cerebral atrophy
Molecular Composition of the Hallmark Lesions of Alzheimer’s Disease

- **Neurofibrillary tangles**
  - Intracellular (neurons)
  - Contain paired helical filaments comprised of the microtubule associated protein tau which is abnormally phosphorylated
  - Biochemically insoluble

- **Amyloid plaques**
  - Extracellular
  - Contain straight fibrils comprised of Aβ
    - i.e. 39-42 amino acid long peptides which is cleaved from the β-amyloid precursor proteins (APPs)
  - Biochemically insoluble
Neurofibrillary tangle
Neurofibrillary tangles

Neuritic threads

Immunohistochemical stain for phosphorylated tau
**Paired helical filament-Tau**

- **MAPT** (Chr 17q21): normal tau protein binds to and stabilizes microtubules
- Insoluble
- Mainly found in neuronal cell bodies and dendrites
- Aberrantly hyperphosphorylated at many serine and threonine residues
- Pathologic tau is unable to bind to microtubules unless it is dephosphorylated *in vitro*

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**A68: A Major Subunit of Paired Helical Filaments and Derivatized Forms of Normal Tau**

VIRGINIA M.-Y. LEE,* BRAN J. BALIN, LASZLO OTVOS, JR., JOHN Q. TROJANOWSKI

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Fitzpatrick et al., *Nature*, 2017
Falcon et al., *Acta NP*, 2018
Alzheimer’s Disease Plaques

• “Plaques are not made of tau. The 50,000 or so people working on the amyloid cascade hypothesis would consider this statement highly incompetent. To say that Alzheimer saw plaques and tangles where neurons had once been is equally incompetent.”
Neuritic plaques
Alzheimer’s Disease
Amyloid Plaques

- Extracellular deposition of aggregated straight fibrils
- Comprised of 39-42 amino acid long Aβ peptides cleaved from amyloid precursor protein (APP)
Alzheimer’s Disease
Diverse Morphology of Amyloid Plaques
Neuroimaging: Amyloid PET

JAMA, January 19, 2011—Vol 305, No. 3  275

Use of Florbetapir-PET for Imaging β-Amyloid Pathology

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Michael J. Krautkramer, BS
Hank E. Kung, PhD
R. Edward Coleman, MD
P. Murali Doraiswamy, MD
Adam S. Fleisher, MD, MAS
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Erie M. Reiman, MD
Simone P. Zeltner, PhD
Daniel M. Skovronsky, MD, PhD
for the AV45-A07 Study Group
Thank you!

j/k
Part II:
NIA-AA Alzheimer’s Disease Neuropathology Criteria
National Institute on Aging–Alzheimer’s Association guidelines for the neuropathologic assessment of Alzheimer’s disease

Bradley T. Hyman, Creighton H. Phelps, Thomas G. Beach, Eileen H. Bigio, Nigel J. Cairns, Maria C. Carrillo, Dennis W. Dickson, Charles Duynakaerts, Matthew P. Frosch, Eliezer Masliash, Suzanne S. Mirra, Peter T. Nelson, Julie A. Schneider, Dietmar Rudolf Thal, Bill Thies, John Q. Trojanowski, Harry V. Vinters, Thomas J. Montine

Alzheimer’s & Dementia 8 (2012) 1–13

↑

NIA-Reagan Criteria (1997)

↑

CERAD (1991)

↑

Khachaturian Criteria (1984)
NIA-AA Criteria: Conceptual Change

• Prior NIA-Reagan criteria resulted in a probability statement about how likely the observed neuropathologic change was associated with clinical AD (low, intermediate, high \textit{probability})

• Current NIA-AA criteria reports the amount of AD neuropathologic change (ADNC) irrespective of clinical data (low, intermediate high \textit{level of ADNC})

• Presence of atherosclerosis defines cardiovascular disease, does not require symptoms such as angina, myocardial infarction

• Presence of ADNC defines Alzheimer’s disease irrespective of clinical syndrome
"ABC" Score

<table>
<thead>
<tr>
<th>AD neuropathologic change</th>
<th>A&lt;sup&gt;b&lt;/sup&gt;</th>
<th>C&lt;sup&gt;c&lt;/sup&gt;</th>
<th>B&lt;sup&gt;a&lt;/sup&gt;</th>
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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
Braak Stages of Neurofibrillary Degeneration

a  stage I  b  stage II  c  stage III

transentorhinal region  hippocampus
rhinal sulcus

transentorhinal region
entorhinal region

occipitotemporal gyrus
temporal neocortex
transentorhinal region

Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry

Heiko Braak - Irina Alafuzoff - Thomas Arzberger - Hans Kretzschmar - Kelly Del Tredici
Braak Stages of Neurofibrillary Degeneration

Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry

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Braak Stages of Neurofibrillary Degeneration

Braak Staging

Hippocampus (at the level of the LGN) 

Braak I
Braak II
Braak III
Braak IV

Striate (visual) and peristriate cortex

Braak 0-IV
Braak V
Braak VI
Biochemical Classification of Tauopathies

Trojanowski and Lee, 2001

Gibbons et al., 2019
A: Thal Phase (Amyloid)

### Table Percentage of cases exhibiting Aβ-depots

<table>
<thead>
<tr>
<th>Region</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
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<tbody>
<tr>
<td>Neocortex</td>
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<td>Basal Ganglia</td>
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<td>Amygdala</td>
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<td>Thalamus</td>
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<tr>
<td>Hypothalamus</td>
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<tr>
<td>Basal Forebrain nuclei (Meynert)</td>
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<td>CA1</td>
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<td>Central Gray</td>
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<td>Superior Collicle</td>
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<td>Red Nucleus</td>
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<tr>
<td>Inferior Olivary Nucleus</td>
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<td>Substantia nigra</td>
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<tr>
<td>Reticular formation of the medulla oblongata</td>
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<tr>
<td>Cerebellar molecular layer</td>
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<tr>
<td>Reticular formation of the pons</td>
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<tr>
<td>Anterior and central raphe nuclei</td>
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<td>loopus oculi</td>
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<tr>
<td>Parabrachial nucleus</td>
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<tr>
<td>Reticulo tegmental nucleus (Bechterew)</td>
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<td>Dorsal tegmental nuclei (Gudzlen)</td>
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<td>Nuclei pontis</td>
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<tr>
<td>Cerebellar granule cell layer</td>
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<tr>
<td>Dentate nucleus</td>
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Regions exhibiting Aβ deposits in phase 1 are A2 and A3; phase 4 in 40% gray; and those in phase 5 in 20% gray.
C: CERAD (Neuritic Plaques)

Figure 1. This diagram of the lateral surface of the brain illustrates the areas of neocortex from which recommended neocortical sections are taken.

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease

S.B. Mina, MD; A. Heyman, MD; D. McKhail, MD; J.M. Ueda, MD; B.J. Ousby, MD, PhD.
L.K. Brownlee, BChir, MD; P.R. Vogel, MD; J.S. Hughes, MD; G. suma Bella, PhD; L. Frang, MD;
and participating CERAD neuropathologists.

Figure 2. Senile plaques (neuritic) per 100X microscopic field. This cartoon provides a guide to semiquantitative assessment of plaque density per square millimeter.
<table>
<thead>
<tr>
<th>AD neuropathologic change</th>
<th>B&lt;sup&gt;a&lt;/sup&gt;</th>
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II. “Alzheimer’s Disease”
Heterogeneity
Dementia

Progressive memory dysfunction

Stepwise neurologic decline

Cerebrovascular disease

Behavioral/Personality changes

Language dysfunction

TDP-43

Tau

Amyloid plaques

Neurofibrillary tangles

Lewy Bodies

Movement disorder

Weakness, spasticity

TDP-43

Dementia
Co-morbid Neurodegenerative Disease Pathologic Change

Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated

Robinson JL, et al., Brain 141: 2181-2193, 2018
TDP-43 & Hippocampal Sclerosis and Risk for AD Dementia

<table>
<thead>
<tr>
<th>Neuropathological indices</th>
<th>Fraction attributable % (95% CI)(^a)</th>
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<tbody>
<tr>
<td>Alzheimer’s disease (ADNC)</td>
<td>39.4 (31.5–47.4)</td>
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<tr>
<td>Vascular disease pathology(^b)</td>
<td>24.8 (17.3–32.1)</td>
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<tr>
<td><strong>LATE-NC</strong></td>
<td><strong>17.3 (13.1–22.0)</strong></td>
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<tr>
<td>(\alpha)-Synucleinopathy/Lewy body pathology</td>
<td>11.9 (8.4–15.6)</td>
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</tbody>
</table>

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Brain, 2019
Vascular Dementia

- Multi-infarct dementia
- Subcortical vascular dementia
- Strategic infarct dementia
- Step-wise decline with clinical phenotype depending on vascular territory that is affected

From www.radiopaedia.org
Microscopic Neuropathology of Frontotemporal Lobar Degeneration

TDP-43
(TAR DNA Binding protein of 43 kDa)

Tau

(FUS)
Fused-In-Sarcoma
FTLD-TDP Subtypes

<table>
<thead>
<tr>
<th></th>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
<th>Type D</th>
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<td>White Matter</td>
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</table>

Expansion of the classification of FTLD-TDP: distinct pathology associated with rapidly progressive frontotemporal degeneration

Edward B. Lee, Silvia Porta, G. Michael Bae, Yan Xu, EunRan Sul, Linda K. Kwong,
Diseases with TDP-43 Pathology

- Frontotemporal lobar degeneration with TDP-43 inclusions
- Amyotrophic lateral sclerosis
- Limbic-predominant Age-related TDP-43 Encephalopathy
- Corticobasal degeneration
- Trauma RElated NeuroDegeneration
- Parkinsonism-dementia complex of Guam
- Perry syndrome
- Alexander’s disease
Limbic-predominant Age-related TDP-43 Encephalopathy (LATE-NC)

<table>
<thead>
<tr>
<th>Simplified staging of TDP-43 proteinopathy* for routine LATE-NC diagnosis (consensus recommendation)</th>
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<tr>
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Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Brain, 2019
Lewy Body Disease (PD, PDD, DLB): $\alpha$-synuclein

- 8-30μm neuronal cytoplasmic inclusions with a hyaline eosinophilic core and a pale halo
- Small, soluble protein of 140 amino acids
- Member of a diverse family of synaptic proteins
- Enriched in presynaptic terminals of neurons may function in synaptic transmission
Diseases with $\alpha$-Synuclein Pathology

- Parkinson’s disease
- Parkinson’s disease dementia
- Dementia with Lewy bodies
- “Lewy body variant of Alzheimer’s disease”
  - Combined AD and DLB pathology
- Multiple System Atrophy
- Neurodegeneration with brain iron accumulation 1 (formerly HS-disease)
- Diseases with variable $\alpha$-synuclein pathology
  - Down’s syndrome
  - Sporadic and familial Alzheimer’s disease
  - Guam parkinsonism-dementia complex
# Lewy Body Disease Patterns

## Diagnosis and management of dementia with Lewy bodies

*Third report of the DLB consortium*

<table>
<thead>
<tr>
<th>Lewy body type pathology</th>
<th>Brainstem regions</th>
<th>Basal forebrain/limbic regions</th>
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<tbody>
<tr>
<td></td>
<td>IX-X</td>
<td>LC</td>
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<tr>
<td>Brainstem-predominant</td>
<td>1-3</td>
<td>1-3</td>
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<tr>
<td>Limbic (transitional)</td>
<td>1-3</td>
<td>1-3</td>
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<tr>
<td>Diffuse neocortical</td>
<td>1-3</td>
<td>1-3</td>
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1 (mild)  2 (moderate)  3 (severe)  4 (very severe)
Lewy Body Disease: Unique CA2 Predilection
III. The Ultimate Diagnosis: Reporting Autopsy Results
Integrated Neurodegenerative Disease Autopsy Report

1. Macroscopic (gross) description

2. Microscopic description

   “We stained XYZ and we saw ABC, etc.”

3. Pathologic diagnosis

   High level of Alzheimer’s disease neuropathologic change (A3, B3, C3)
   Lewy body disease, transitional pattern
   Limbic-predominant age-related TDP-43 encephalopathy (LATE), Stage 3

4. Clinicopathologic correlation

   “This x year old male had a clinical history of dementia with Lewy bodies. We saw xyz which correlates well with the history of dementia, etc.

5. Final integrated diagnosis
Let’s look at a few cases...
Integrated Neurodegenerative Disease Autopsy Report

• Alzheimer’s disease, posterior cortical atrophy variant
  • Histologic diagnosis: High level of Alzheimer’s Disease neuropathologic change (A3, B3, C3)
  • Co-morbid pathology: LATE-NC (Stage 2)
  • Clinical classification: Posterior cortical atrophy
  • Biochemical data: 3R+4R tauopathy
  • Molecular data: *APOE* E3/E4, *TREM2* p.R47H
Autopsy: Final Comprehensive Disease Classification

- Progressive memory dysfunction
- Amyloid plaques
- Neurofibrillary tangles
- Vascular-mediated brain injury
- Stepwise neurologic decline
- TDP-43
- Tau
- Lewy Bodies & Neurites
- Behavioral/Personality changes
- Language dysfunction
- Weakness, spasticity
- Dementia
- Movement disorder
Thank you!

Q&A