Tauopathies

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Disclosures

• I have no relevant financial relationships to disclose
Learning Objectives

1. Discuss the normal structure of tau and the alterations that can occur in tauopathies
2. Explain the role of immunohistochemistry in distinguishing between the various tauopathies
3. List the neuropathologic features that distinguish primary age-related tauopathy from Alzheimer disease
4. List the unique diagnostic lesions that characterize each of the major subtypes of FTLD-tau
Tauopathies: Definition

• Disorders characterized by the presence of aggregates of abnormal tau protein that are deposited in CNS neurons, glia, or both, and are associated with neurodegeneration

• Tauopathies may manifest with progressive but variable clinical signs and symptoms that primarily include cognitive impairment, movement disorder (especially Parkinsonism), or both

• Clinical deficits are not required for a diagnosis of tauopathy
Tau protein: basic features

- Classification: microtubule-associated protein (MAP)
- Function: assembly and stabilization of the axonal cytoskeleton through its interaction with tubulin, regulated by phosphorylation
- Encoded on human chromosome 17 (MAPT gene)
  - 6 isoforms resulting from alternative splicing of pre-mRNA of exons 2, 3, and 10
Tau protein: isoforms

N-terminal inserts and MT-binding repeats for different isoforms of tau protein:

- 3-repeat tau
- 4-repeat tau

MT-BINDING DOMAIN
Classification of tauopathies

• Primary
  – May be genetic or sporadic/idiopathic
  – Usually restricted to 3R or 4R tau lesions

• Secondary
  – May be genetic or sporadic/idiopathic
  – Alzheimer disease
    • Tauopathy results from Aβ toxicity
  – ALS/PD-Guam
    • Toxic/environmental
  – CTE
    • Environmental
Classification of tauopathies (continued)

- Genetics
  - Most are sporadic
  - MAPT mutations (FTDP-17) account for a small subset of cases
    - Exonic or intronic
    - Missense
    - Deletions
  - Most genetic forms mimic neuropathology of sporadic forms
Classification of tauopathies (continued)

• Neuropathology
  – Lesion morphology
  – Cell type involvement
  – Distribution of lesions

• Tau isoforms (3R, 4R or 3R+4R), typically by IHC

• Cryoelectron microscopy reveals disease-specific conformational folds of tau filaments
Tau post-translational modifications (PTM)

- Phosphorylation
- Acetylation
- Ubiquitylation
- Glycation
- Glycosylation
- Methylation
- Oxidation
- Proteolysis
- Abnormal ratio of tau isoforms
Entities discussed

• Alzheimer disease and AD-like disorders
  – AD/ADNC
  – PART

• FTLD-tau
  – Pick disease
  – CBD
  – PSP

• Glial tauopathy
  – GGT
Alzheimer disease and AD-like disorders
Alzheimer disease (AD)

History

- Alois Alzheimer (1907): “A characteristic disease of the cerebral cortex”
Alzheimer disease (AD)
Clinical features (Alzheimer-type dementia)

• Dementia: generalized deterioration in multiple cognitive domains
  • Memory
  • Language
  • Concentration
  • Orientation
  • Executive function
Alzheimer disease (AD)
Neuropathologic diagnostic criteria

• Khachaturian (1985), CERAD (1991) relied on senile plaque density

• NIA/Reagan Institute (1997) required senile plaques and neurofibrillary tangles

  • All of the above criteria were applied to determine “likelihood that dementia was due to AD lesions”
AD -> Alzheimer disease neuropathologic change (ADNC)

• NIA/Alzheimer’s Association Criteria (2012)
  – distinguished “AD neuropathologic change” from the clinico-pathologic term “AD”
  – such changes may be present in subjects with normal cognition (“preclinical AD”), MCI, and dementia
Alzheimer disease neuropathologic change (ADNC)

**Table 2** “ABC” score for AD neuropathologic change

<table>
<thead>
<tr>
<th>“A”</th>
<th>Thal Phase for Aβ plaques [57]</th>
<th>“B”</th>
<th>Braak and Braak NFT stage [14,15]</th>
<th>“C”</th>
<th>GERAD neuritic plaque score [41]</th>
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</thead>
<tbody>
<tr>
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<td>0</td>
<td>0</td>
<td>None</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>1 or 2</td>
<td>1</td>
<td>I or II</td>
<td>1</td>
<td>Sparse</td>
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<tr>
<td>2</td>
<td>3</td>
<td>2</td>
<td>III or IV</td>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>4 or 5</td>
<td>3</td>
<td>V or VI</td>
<td>3</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

**Table 3** “ABC” score for level of AD neuropathologic change

<table>
<thead>
<tr>
<th>AD neuropathologic change</th>
<th>B&lt;sup&gt;a&lt;/sup&gt;</th>
<th>0 or 1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&lt;sup&gt;b&lt;/sup&gt; C&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>Not&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Not&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Not&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td>0 or 1</td>
<td>Low&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Low&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Low&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>2 or 3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Low&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Intermediate&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Intermediate&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Any C</td>
<td>Low&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Intermediate&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Intermediate&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>A&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Low&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Intermediate&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
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<td>2 or 3</td>
<td>Low&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Intermediate&lt;sup&gt;e&lt;/sup&gt;</td>
<td>High&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

AANP
Alzheimer disease neuropathologic change (ADNC)

Tau isoforms

- $3R + 4R$, approximately equal proportions

- Neurofibrillary tangle
- Dystrophic neurites
- Senile plaque
Primary age-related tauopathy (PART)

**History**

- In the shadow of pre-2012 criteria for “AD,” problems were encountered in clinico-pathologic correlation for subjects with:
  - Clinical diagnosis of cognitive impairment or dementia
  - AD-like neurofibrillary tangles, but confined to medial temporal lobe (entorhinal cortex and hippocampus)
  - No neuritic plaques - therefore did not satisfy 1997 NIA/Reagan Institute criteria for AD (nor 2012 NIA/AA criteria for ADNC)
  - No other explanation for cognitive impairment
Primary age-related tauopathy (PART): a common pathology associated with human aging

John F. Crary · John Q. Trojanowski · Julie A. Schneider · Jose F. Abisambra · Erin L. Abner · Irina Alafuzoff · Steven E. Arnold · Johannes Attems · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Marla Gearing · Lea T. Grinberg · Patrick R. Hof · Bradley T. Hyman · Kurt Jellinger · Gregory A. Jicha · Gabor G. Kovacs · David S. Knopman · Julia Kofler · Walter A. Kukull · Ian R. Mackenzie · Eliezer Masliah · Ann McKee · Thomas J. Montine · Melissa E. Murray · Janna H. Neltner · Ismael Santa-Maria · William W. Seeley · Alberto Serrano-Pozo · Michael L. Shelanski · Thor Stein · Masaki Takao · Dietmar R. Thal · Jonathan B. Toledo · Juan C. Troncoso · Jean Paul Vonsattel · Charles L. White 3rd · Thomas Wisniewski · Randall L. Woltjer · Masahito Yamada · Peter T. Nelson
Primary age-related tauopathy (PART)

Neuropathology

• Diagnostic criteria
  – NFT with no (or very little) amyloid or neuritic plaques

• Tau isoforms
  – 3R/4R (i.e., ADNC-like)

• Lesion distribution
  – Braak NFT stage ≤ IV
Primary age-related tauopathy (PART)
Unique hippocampal neuropathology

Original Article

Early Selective Vulnerability of the CA2 Hippocampal Subfield in Primary Age-Related Tauopathy

Jamie M. Walker, MD, PhD, Timothy E. Richardson, DO, PhD, Kurt Farrell, PhD, Megan A. Iida, BS, Chan Foong, MS, Ping Shang, HT(ASCP), Johannes Attems, MD, Gai Ayalon, PhD, Thomas G. Beach, MD, PhD, Eileen H. Bigio, MD, Andrew Budson, MD, Nigel J. Cairns, PhD, María Corrada, ScD, Eitty Cortes, MD, Dennis W. Dickson, MD, Peter Fischer, MD, Margaret E. Flanagan, MD, Erin Franklin, MS, Maria Gearing, PhD, Jonathan Glass, MD, Lawrence A. Hansen, MD, Vahram Haroutunian, PhD, Patrick R. Hof, MD, Lawrence Honig, MD, PhD, Claudia Kawas, MD, C. Dirk Keene, MD, PhD, Julia Kolber, MD, Gabor G. Kovacs, MD, PhD, Edward B. Lee, MD, PhD, Mirjam I. Lutz, MSc, Qinwen Mao, MD, PhD, Eliezer Masliah, MD, Ann C. McKee, MD, Corey T. McMillan, PhD, M. Marsel Mesulam, MD, Melissa Murray, PhD, Peter T. Nelson, MD, PhD, Richard Perrin, MD, PhD, Thao Pham, BS, Wayne Poon, PhD, Dushyanth P. Purohit, MD, Robert A. Rissman, PhD, Kenji Sakai, MD, Mary Sano, PhD, Julie A. Schneider, MD, Thor D. Stein, MD, PhD, Andrew F. Teich, MD, PhD, John Q. Trojanowski, MD, PhD, Juan C. Troncoso, MD, Jean-Paul Vonsattel, MD, Sandra Weintraub, PhD, David A. Wolk, MD, Randall L. Woltrer, MD, PhD, Masahito Yamada, MD, PhD, Lei Yu, PhD, Charles L. White III, MD, and John F. Cray, MD, PhD
Primary age-related tauopathy (PART)
Entorhinal cortex ghost tangles

3R tau
Primary age-related tauopathy (PART)
Clinical features

• Especially common in the “oldest old”
• Not associated with overrepresentation of APOE ε4 allele
• May be associated with normal cognition, amnestic MCI, or dementia
• Clinical features correlate with degree of tau pathology
Fronto-temporal lobar degenerations, tau type (FTLD-tau)
Pick disease (PiD)

History

- Oldest recognized form of FTLD
- Clinical and gross features (lobar atrophy) described by Arnold Pick (1892)
Pick disease (PiD)
History (continued)

- Histopathologic features first described by Alzheimer (1911)
Pick disease (PiD)  
History (continued)  

• Pick disease neuropathologic subtypes of lobar atrophy (Constantinidis et al., 1974)  
  – Type A: Pick bodies present  
  – Type B: ballooned neurons (now likely CBD)  
  – Type C: gliosis and spongiosis (now other FTD subtypes)  
• Pick bodies contain tau (Pollock et al., 1986)  
• Pick tau consists of 3R isoform (Sergeant et al., 1997)
Pick disease (PiD)

Neuropathology

• Diagnostic criteria
  – 3R tau-immunoreactive Pick bodies in dentate gyrus of hippocampus and adjacent cortical areas
Pick disease (PiD)

• Clinical features
  – bvFTD
  – Progressive language disorder
  – Corticobasal syndrome
Corticobasal degeneration (CBD)

History

• First clinicopathologic report by Rebeiz et al. (1967) as “corticodentatonigral degeneration with neuronal achromasia”

• First standardized neuropathologic criteria published in 2002
Corticobasal degeneration (CBD)
Neuropathology

• Diagnostic criteria
  – Neuronal inclusions in cortical and subcortical gray matter
  – Astrocytic plaques in cortex and basal ganglia
  – Threads and coiled bodies in white and gray matter
  – Balloononed neurons

• Tau isoform: 4R
Corticobasal degeneration (CBD)
Corticobasal degeneration (CBD): Gray matter pathology

Cerebral cortex

Hippocampus

Basal ganglia
Corticobasal degeneration (CBD):
White matter pathology
Corticobasal degeneration (CBD): Ballooned neurons

Alpha-B crystallin
Corticobasal degeneration (CBD)  
Clinical features

• Corticobasal syndrome: atypical Parkinsonism
  – Unilateral or asymmetric involuntary movements (rigidity, tremor, dystonia, myoclonus)
  – Apraxia
  – Cortical sensory deficits
  – Alien limb phenomenon
  – Cognitive features typically FTD-type (behavior and language)
  – Often associated with other pathologies, e.g. AD, PiD, PSP, CJD
Progressive supranuclear palsy (PSP)

History

• Described as a clinico-pathologic entity by Richardson, Steele, and Olszewski (1963)

• First standardized neuropathologic diagnostic criteria: NINDS (Hauw et al., 1994)
  – Neurofibrillary tangle distribution in 13 neuroanatomic areas
  – Based primarily on silver staining methods
  – Only moderate inter-rater reliability
  – Did not take all currently recognized lesions into account
Progressive supranuclear palsy (PSP)
Neuropathology: 4R tau

Neurofibrillary tangle
Pretangle
Tufted astrocyte
PSP revised neuropathologic criteria (2022)

Minimum Requirements

- **Neurofibrillary tangles**
  2 of 3 (blue) AND

- **Tufted astrocytes**
  1 of 2 (green)

Rainwater Charitable Foundation criteria for the neuropathologic diagnosis progressive supranuclear palsy

Shana F. Roemer1 · Lea T. Gräber2,3,4 · John F. Cray4 · William W. Seeley1,2 · Ann C. McKee2 · Gabor G. Kovacs2,4 · Thomas G. Beach6 · Charlotte Duckers5,10 · Isidro A. Ferrer1,2 · Ellen Galjø11 · Edward B. Lee11 · Tamas Revesz11 · Charles L. White III12 · Mari Yoshida13 · Felipe L. Pereira14 · Kristen Whitney11 · Nikhil B. Ghapar10 · Dennis W. Dickson14

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Progressive supranuclear palsy (PSP)
Clinical features

- Classically regarded as a Parkinsonian movement disorder
  - Severe postural instability with falls
  - Supranuclear ophthalmoplegia
  - Refractory to anti-Parkinsonian medications
  - Often presents as FTD clinical syndrome
Glial tauopathy
Globular glial tauopathy (GGT)

History

• Characteristic globular inclusions first described by Molina et al. (1998)
  – Temporal lobe biopsy from patient with PPA
  – Glial inclusions immunoreactive for phospho-tau
• Bigio et al. (2001)
  – Detailed findings from autopsy case of patient with atypical FTD presentation
  – “Sporadic multisystem tauopathy” composed of 4R tau isoform by biochemical analysis
Globular glial tauopathy (GGT) Neuropathology

• Diagnostic criteria
  – Globular cytoplasmic inclusions in oligodendroglia and astrocytes
  – Coiled bodies in oligodendroglia

• Tau isoform: 4R
Globular glial tauopathy (GGT)
Neuropathology
Globular glial tauopathy (GGT)
Neuropathology

Astrocytic inclusion

Oligodendrocyte: coiled body
Globular glial tauopathy (GGT)
Clinical features

• Type I: FTD
• Type II: MND
• Type III: FTD+MND
Technical tips

• It is best practice to cut in a standard and comprehensive set of blocks initially, to standardize the workup, maximize opportunity for demonstrating unexpected pathology, and avoid the need to “go back to the bucket”
• Thioflavine-S works very well for AD and PART pathology, but is not sufficient to demonstrate 3R or 4R restricted tau lesions
• A pretreatment protocol using KMnO4 and oxalic acid (Uchihara et al., Brain Pathol 2011; 21:180-188) can eliminate diffuse background neuropil staining often encountered with a commonly used 3R tau antibody
Virtual slide
Thank you!
Q & A