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

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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

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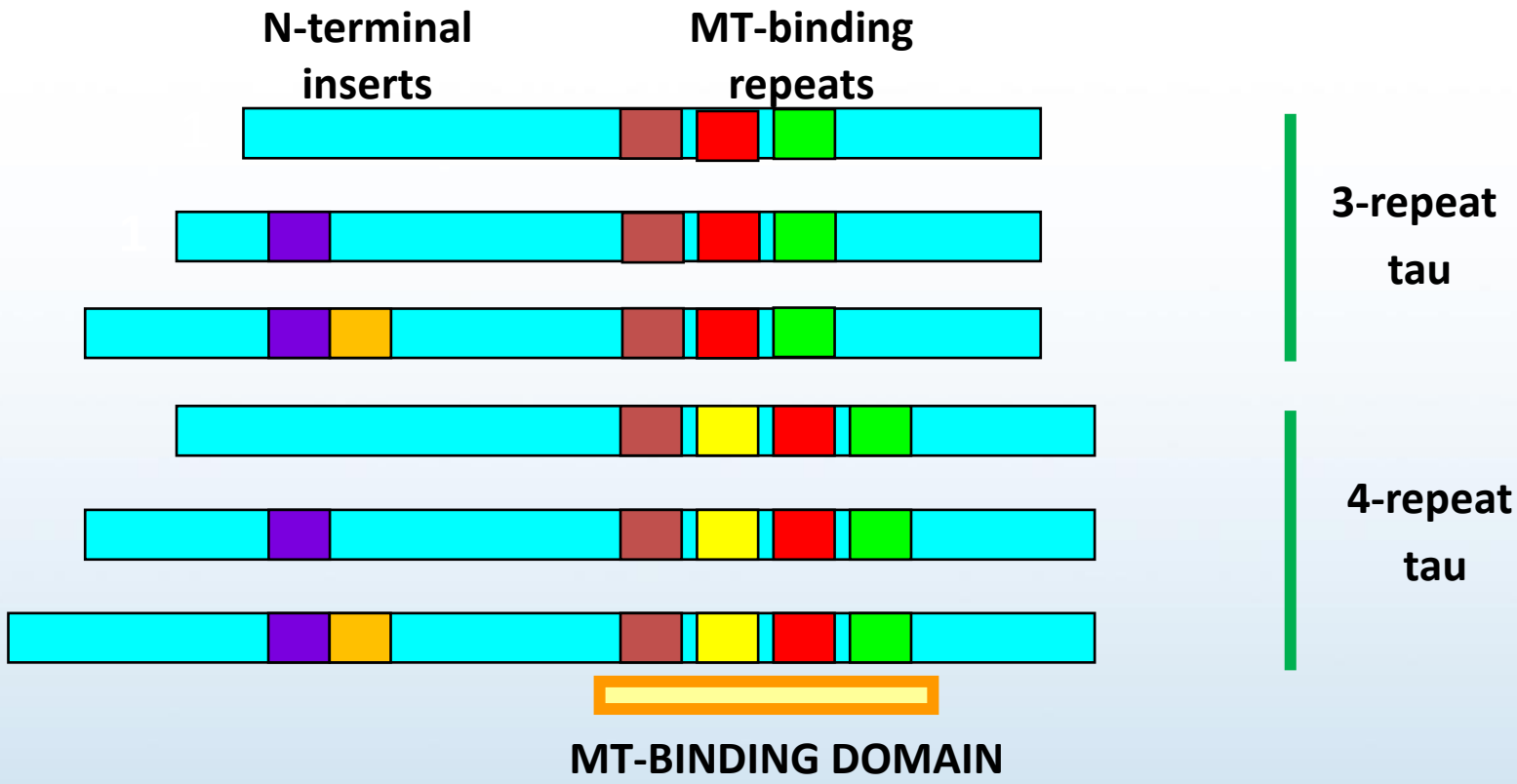
Tau protein: isoforms

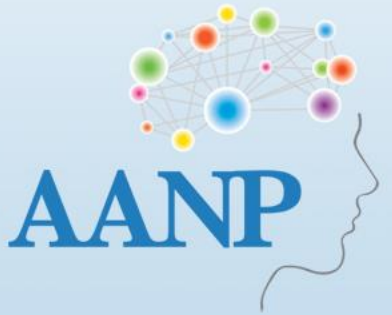


Classification of tauopathies

- 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

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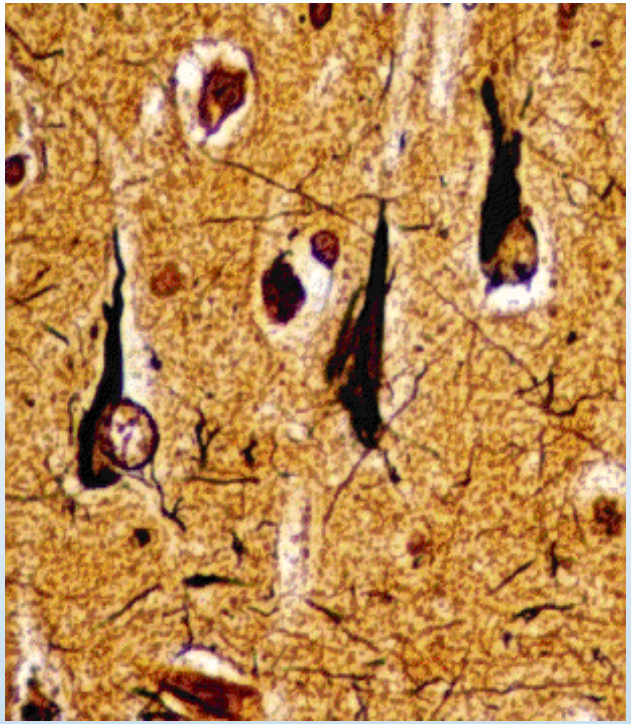
Entities discussed

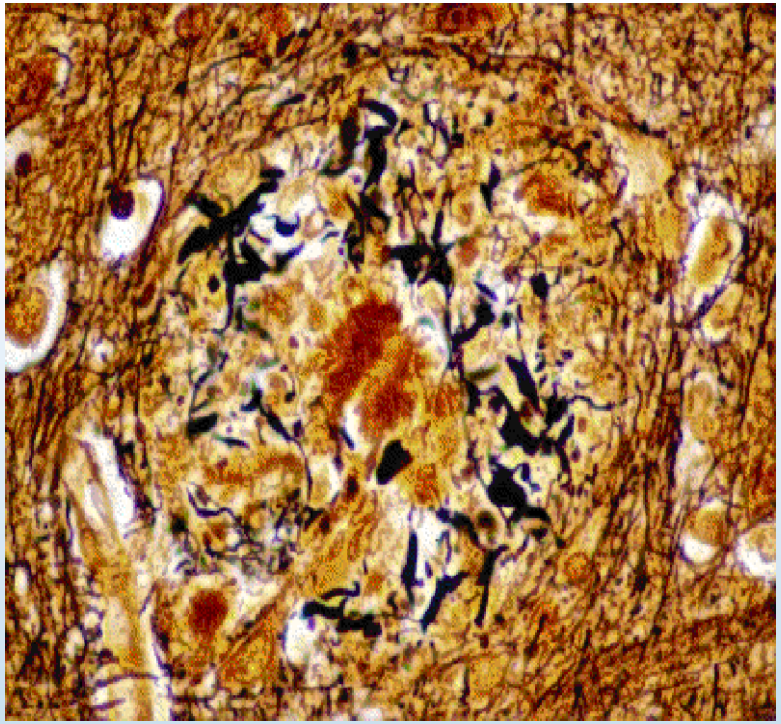
- Alzheimer disease and AD-like disorders
  - AD/ADNC
  - PART
- FTLD-tau
  - Pick disease
  - CBD
  - PSP
- Glial tauopathy
  - GGT

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)

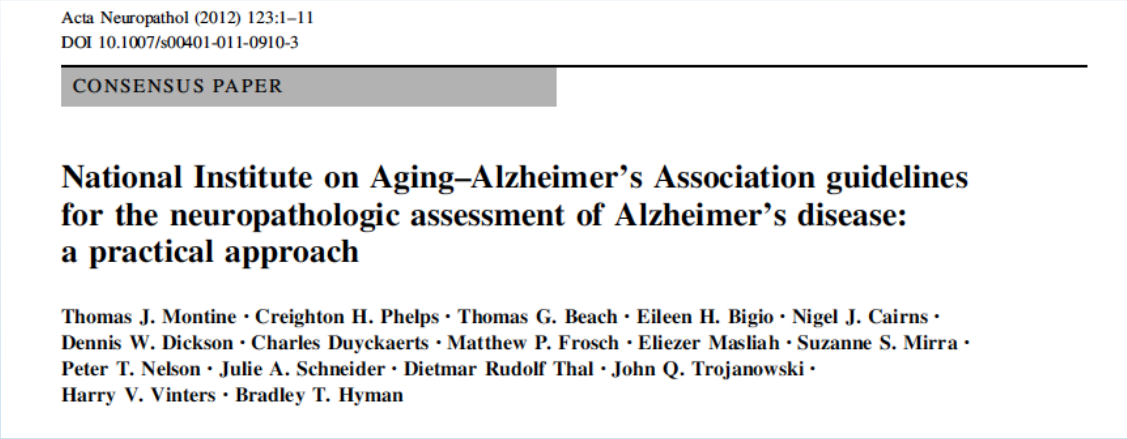
- Dementia: generalized deterioration in multiple cognitive domains
  - Memory
  - Language
  - Concentration
  - Orientation
  - Executive function

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



Acta Neuropathol (2012) 123:1–11
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

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Alzheimer disease neuropathologic change (ADNC)

Table 2 "ABC" score for AD neuropathologic change

"A"	Thal Phase for Aβ plaques [57]	"B"	Braak and Braak NFT stage [14,15]	"C"	CERAD neuritic plaque score [41]
0	0	0	None	0	None
1	1 or 2	1	I or II	1	Sparse
2	3	2	III or IV	2	Moderate
3	4 or 5	3	V or VI	3	Frequent

Table 3 "ABC" score for level of AD neuropathologic change

AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	Not[d]
1	0 or 1	Low	Low	Low[e]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[g]	Intermediate	Intermediate[e]
3	0 or 1	Low[g]	Intermediate	Intermediate[e]
	2 or 3	Low[g]	Intermediate	High

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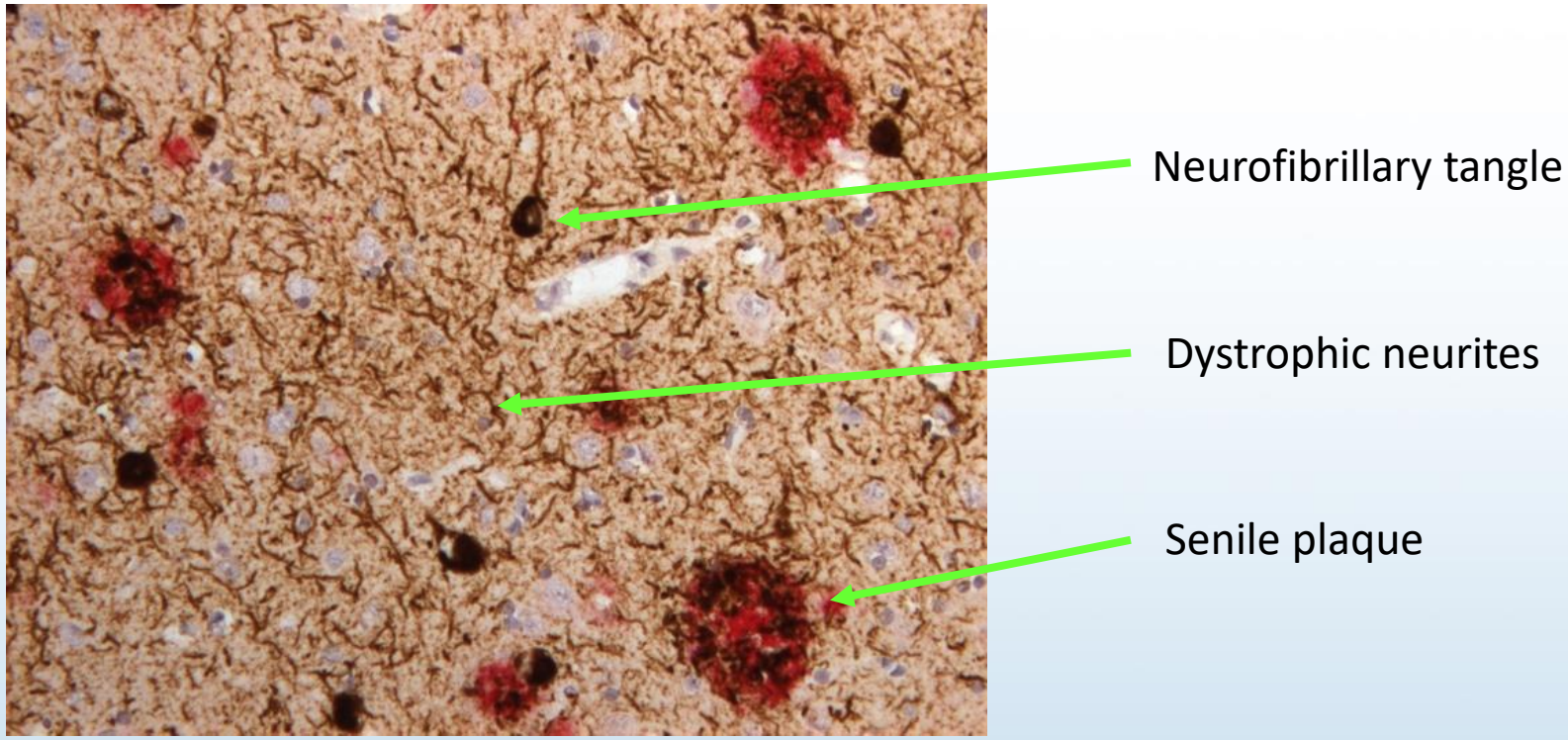
Alzheimer disease neuropathologic change (ADNC)

Tau isoforms

- 3R + 4R, approximately equal proportions



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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

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Primary age-related tauopathy (PART)

Acta Neuropathol (2014) 128:755–766
DOI 10.1007/s00401-014-1349-0

CONSENSUS PAPER

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

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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 $\leq$ IV

Primary age-related tauopathy (PART)
Unique hippocampal neuropathology

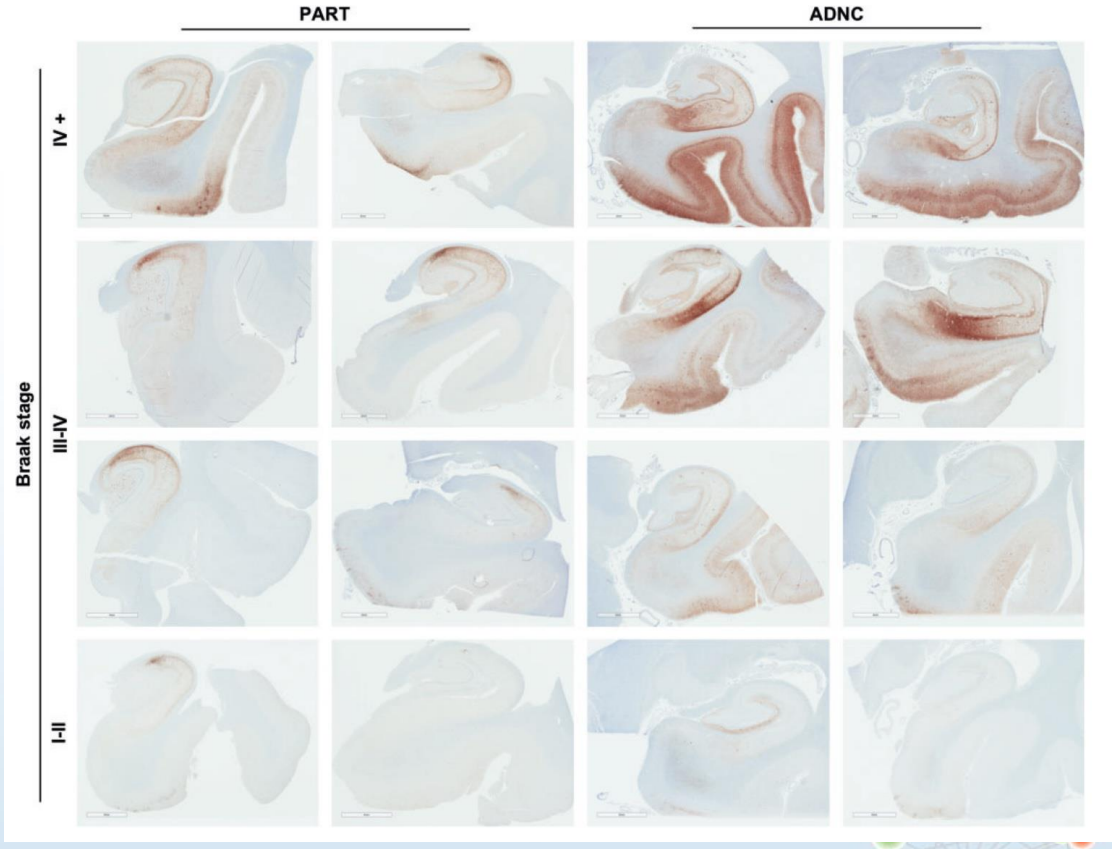
J Neuropathol Exp Neurol
Vol. 80, No. 2, February 2021, pp. 102–111
doi: 10.1093/jnen/nlaa153

OXFORD

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, Etty Cortes, MD, Dennis W. Dickson, MD, Peter Fischer, MD, Margaret E. Flanagan, MD, Erin Franklin, MS, Marla 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 Kofler, 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, Dushyant 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. Woltjer, MD, PhD, Masahito Yamada, MD, PhD, Lei Yu, PhD, Charles L. White III, MD, and John F. Crary, MD, PhD



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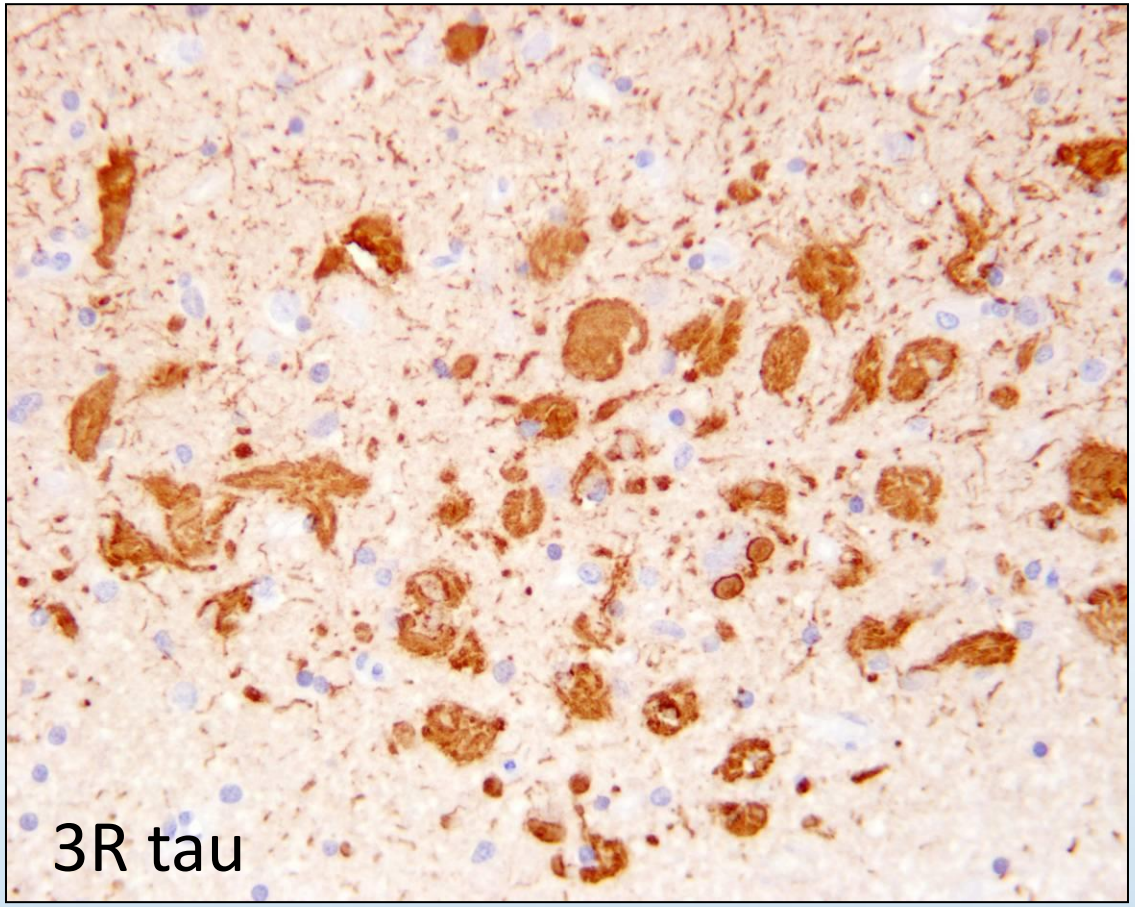
Primary age-related tauopathy (PART)
Entorhinal cortex ghost tangles



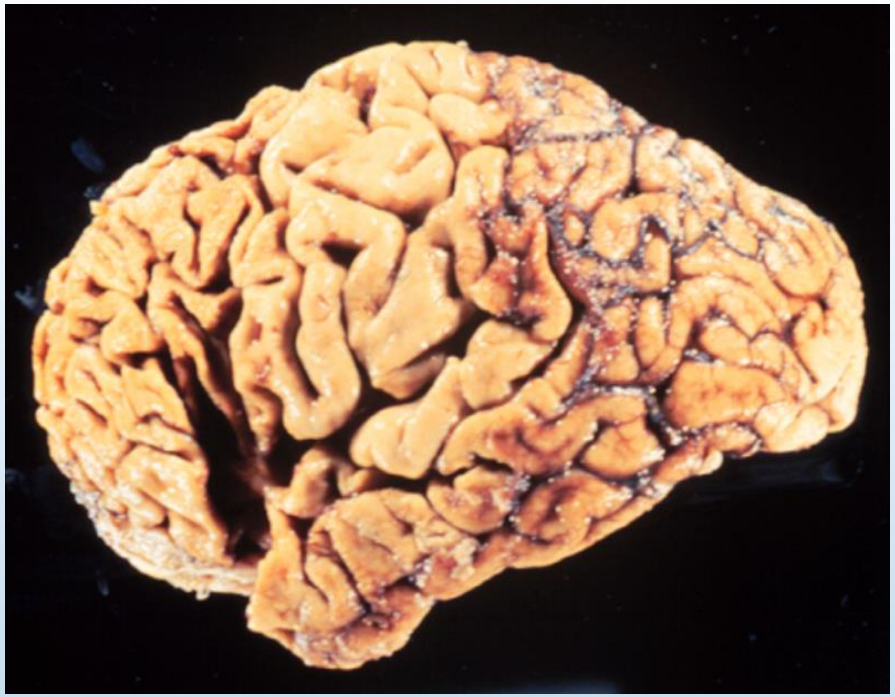
Primary age-related tauopathy (PART)
Clinical features

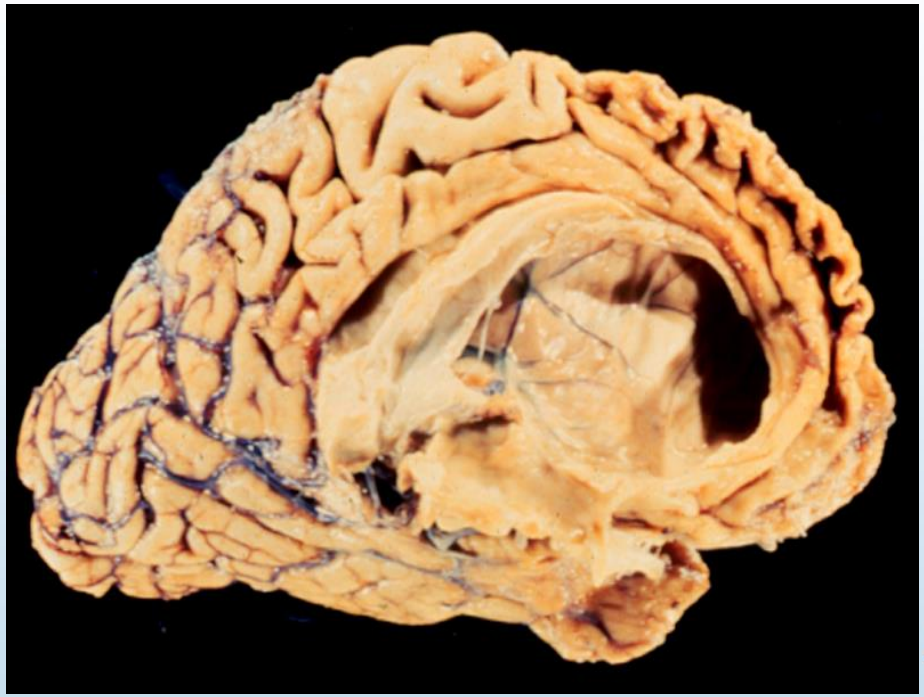
- Especially common in the “oldest old”
- Not associated with overrepresentation of *APOE* ε4 allele
- May be associated with normal cognition, amnestic MCI, or dementia
- Clinical features correlate with degree of tau pathology

Fronto-temporal lobar degenerations, tau type (FTLD-tau)

Pick disease (PiD)
History

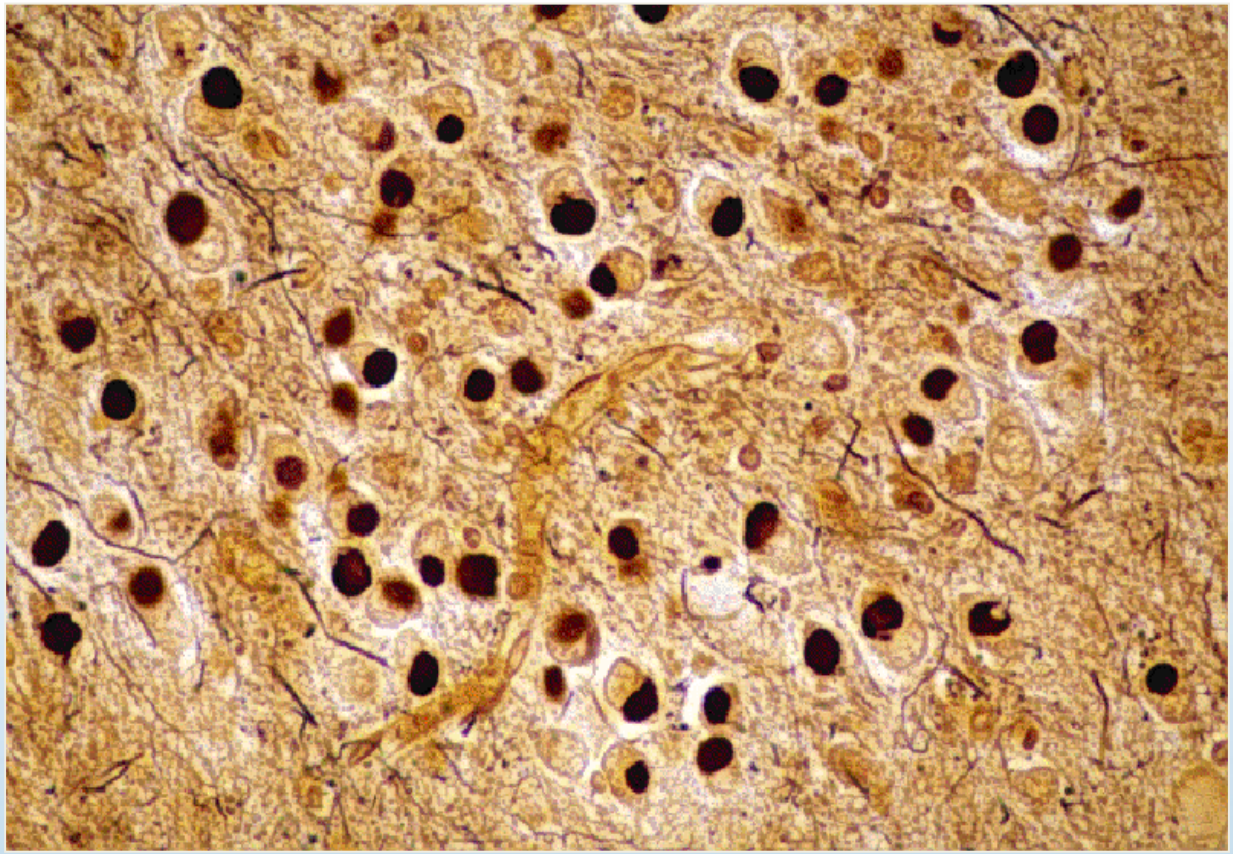
- Oldest recognized form of FTLD
- Clinical and gross features (lobar atrophy) described by Arnold Pick (1892)





Pick disease (PiD)
History (continued)

- Histopathologic features first described by Alzheimer (1911)

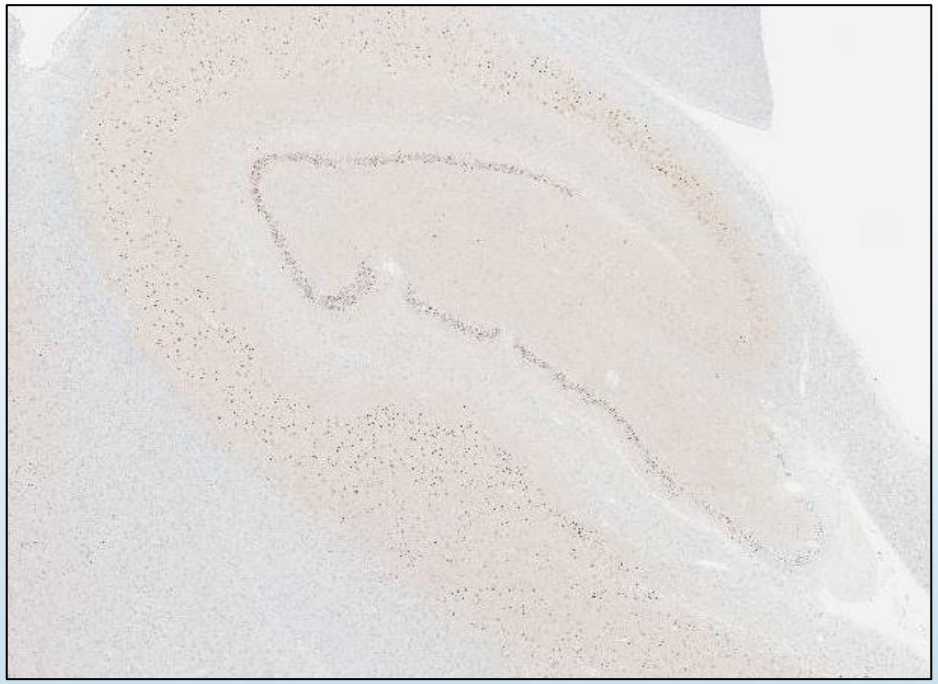


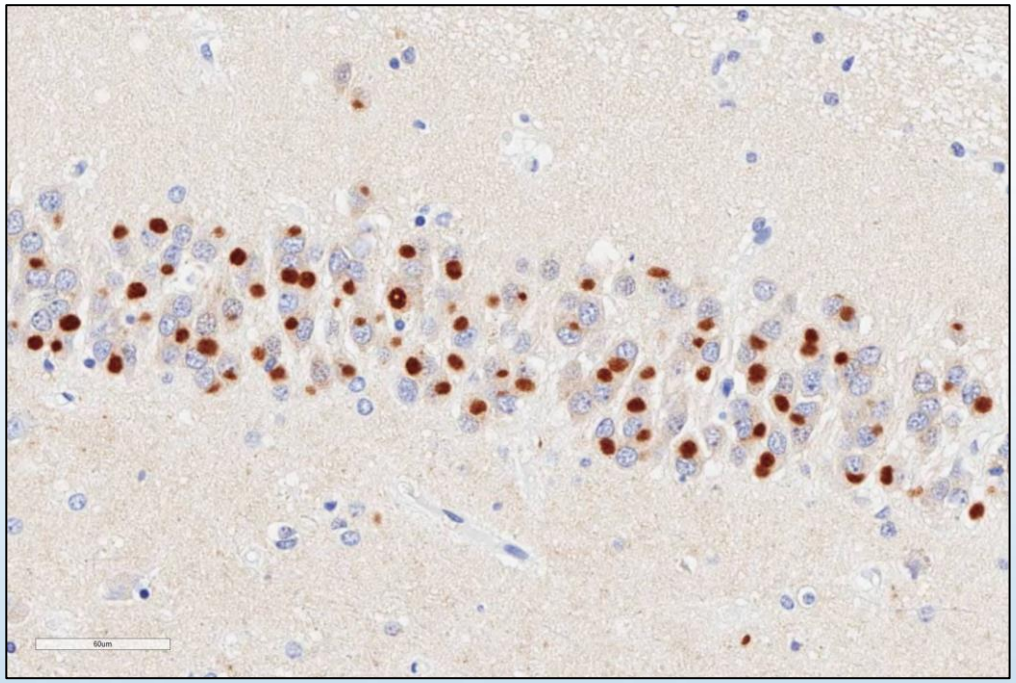
Pick disease (PiD)
History (continued)

- 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



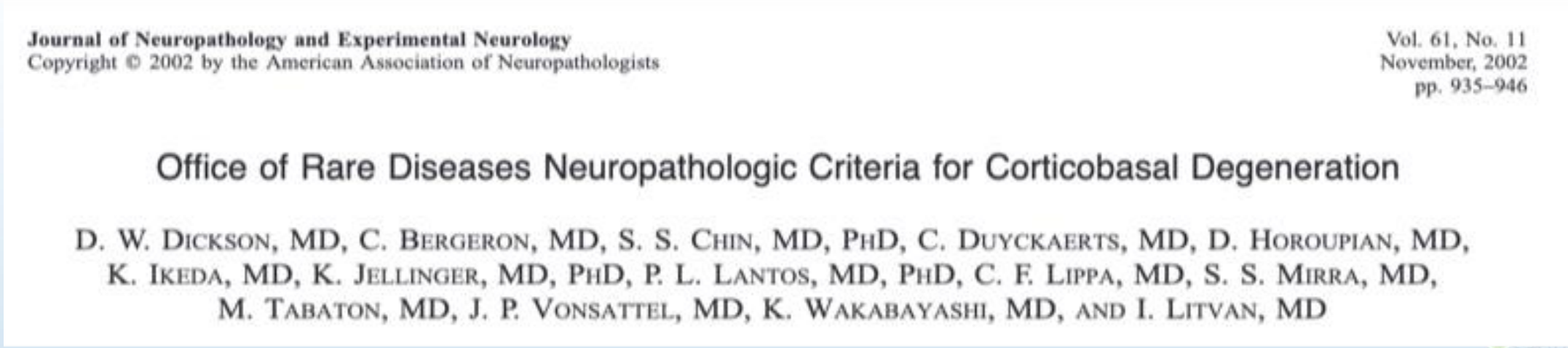


Pick disease (PiD)

- 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



Journal of Neuropathology and Experimental Neurology

Vol. 61, No. 11
November, 2002
pp. 935–946

Office of Rare Diseases Neuropathologic Criteria for Corticobasal Degeneration

D. W. Dickson, MD, C. Bergeron, MD, S. S. Chin, MD, PhD, C. Duyckaerts, MD, D. Horoupian, MD, K. Ikeda, MD, K. Jellinger, MD, PhD, P. L. Lantos, MD, PhD, C. F. Lippa, MD, S. S. Mirra, MD, M. Tabaton, MD, J. P. Vonsattel, MD, K. Wakabayashi, MD, and I. Litvan, MD

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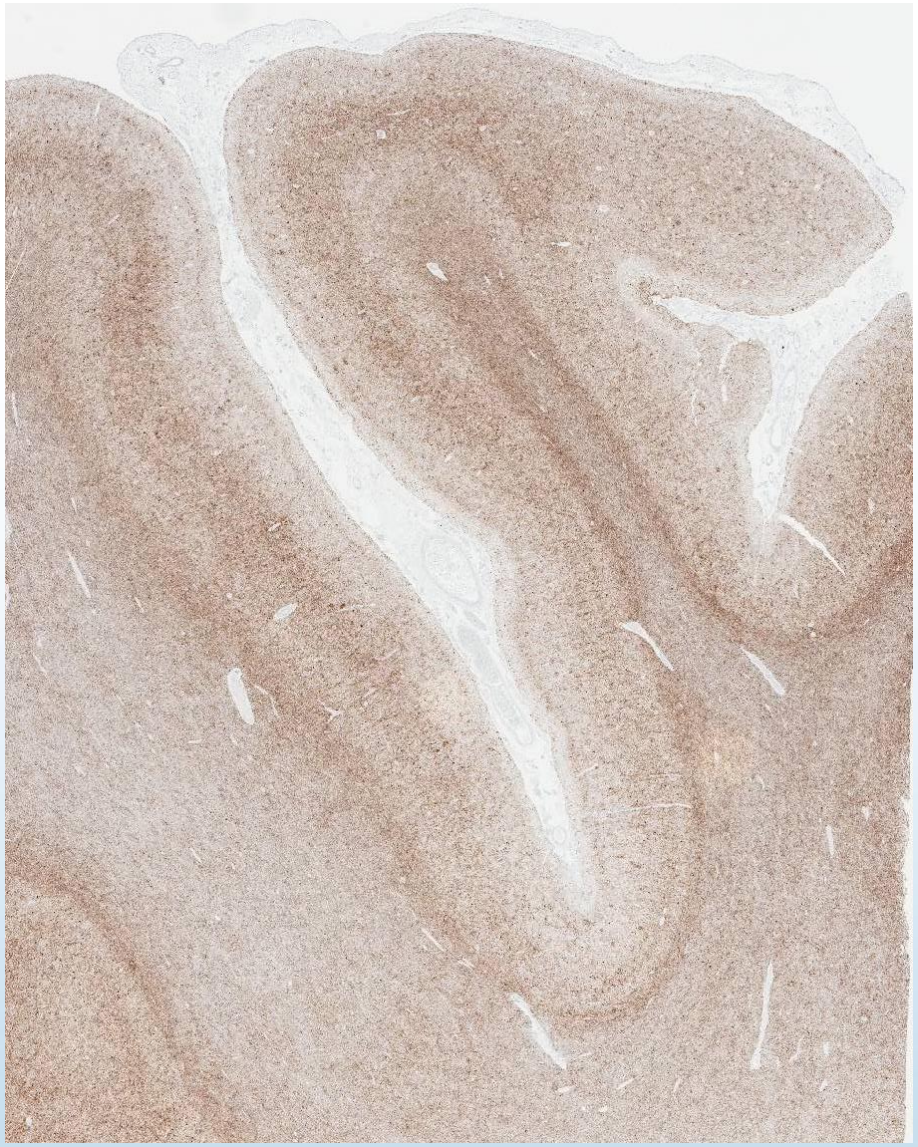
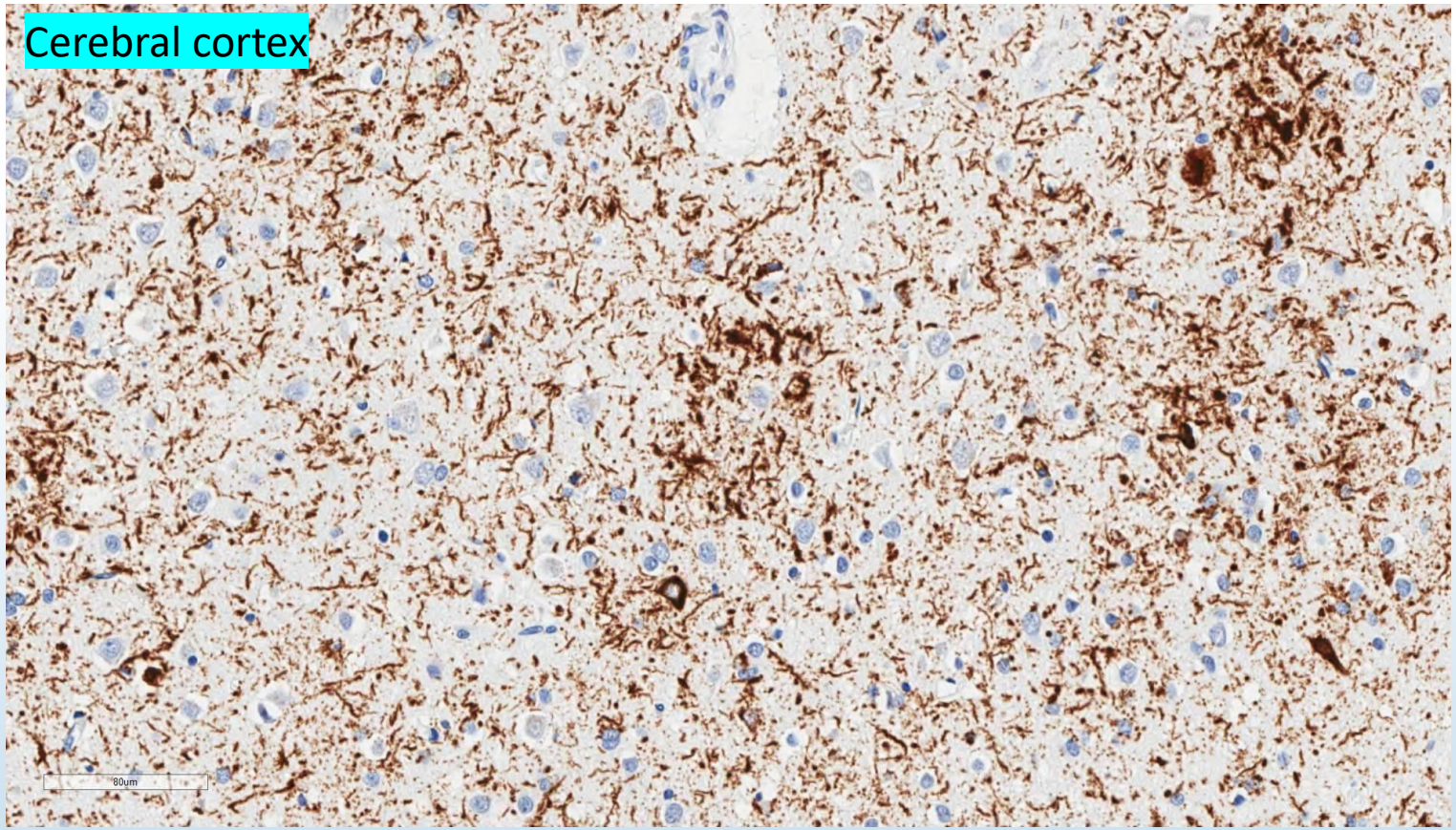
Corticobasal degeneration (CBD)
Neuropathology

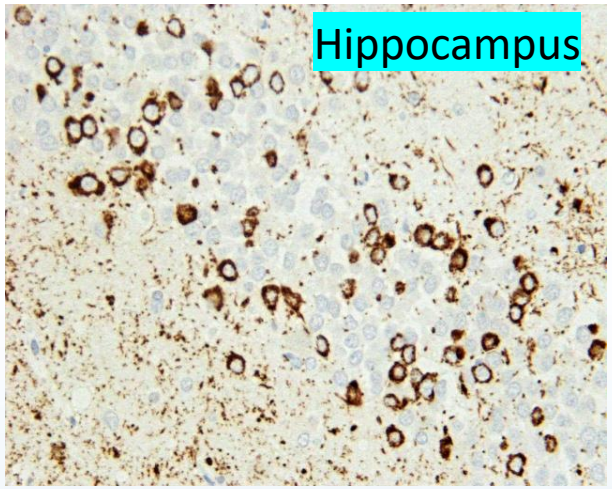
- Diagnostic criteria
  - Neuronal inclusions in cortical and subcortical gray matter
  - Astrocytic plaques in cortex and basal ganglia
  - Threads and coiled bodies in white and gray matter
  - Ballooned neurons
- Tau isoform: 4R

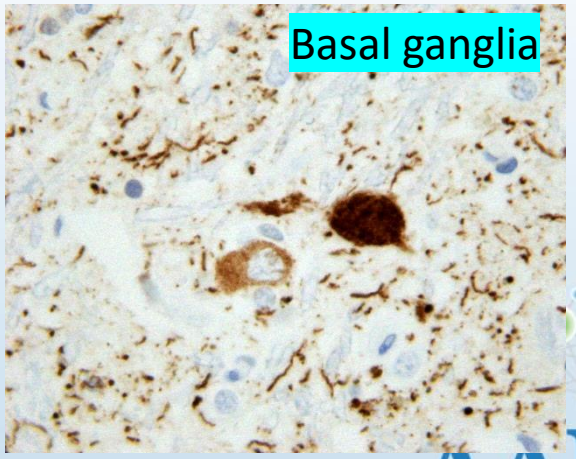
Corticobasal degeneration (CBD)



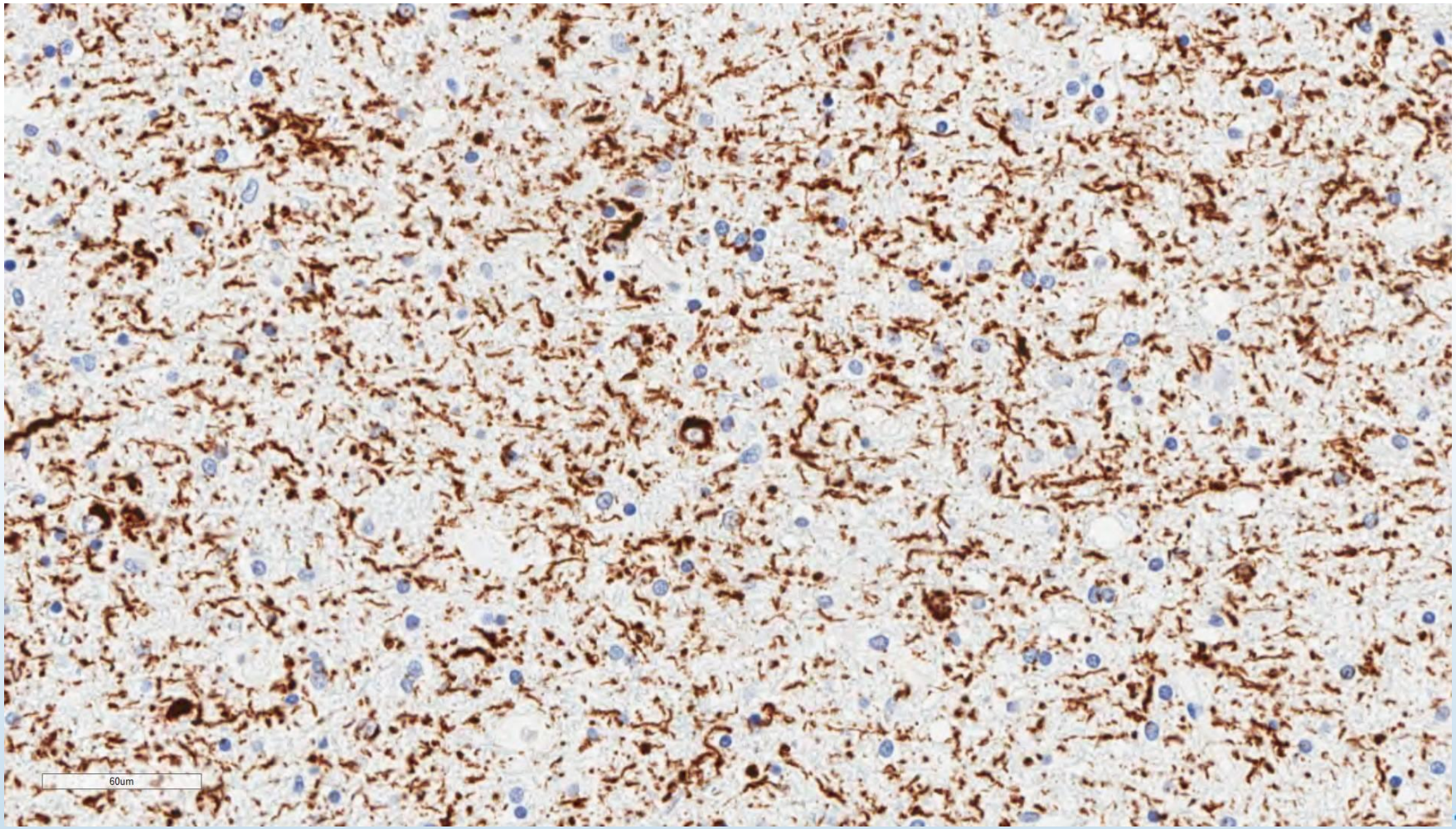
Corticobasal degeneration (CBD): Gray matter pathology







Corticobasal degeneration (CBD): White matter pathology



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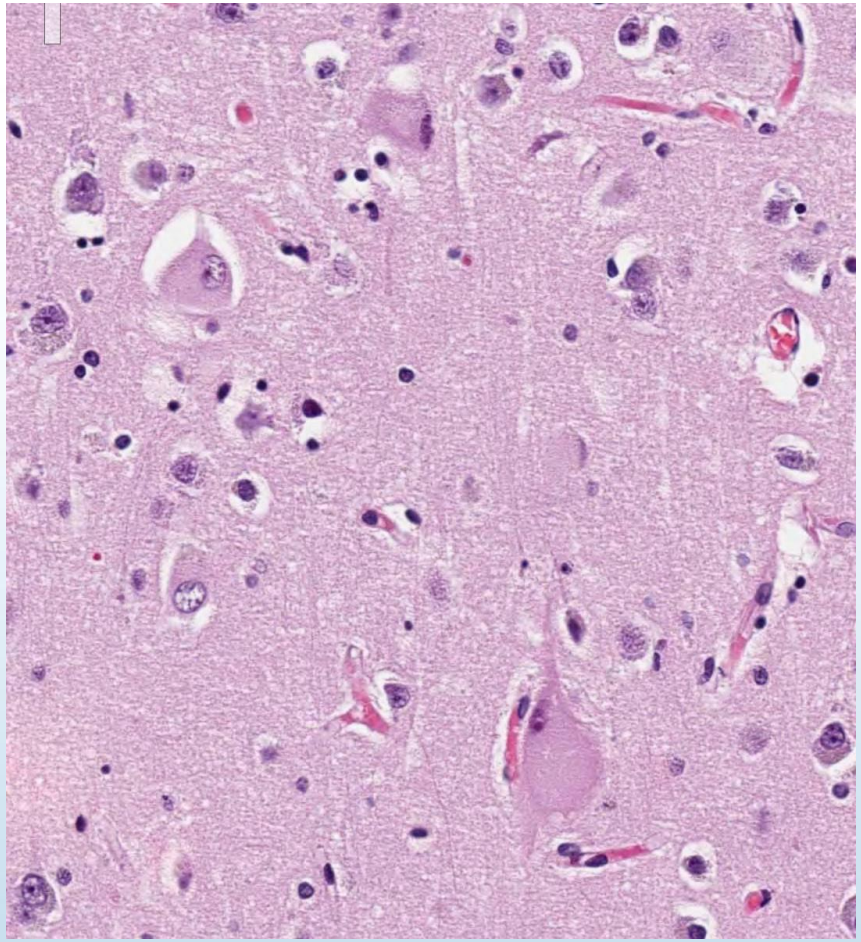
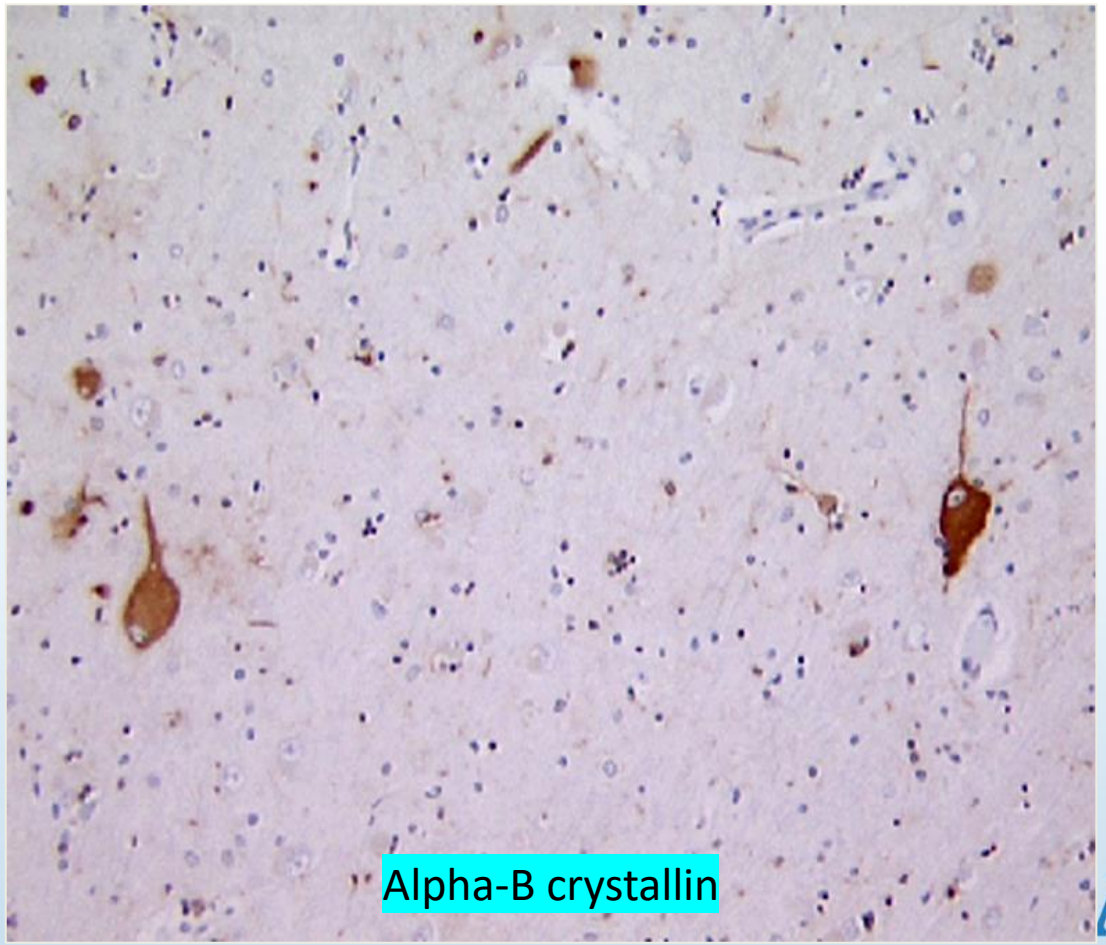
Corticobasal degeneration (CBD): Ballooned neurons





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

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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

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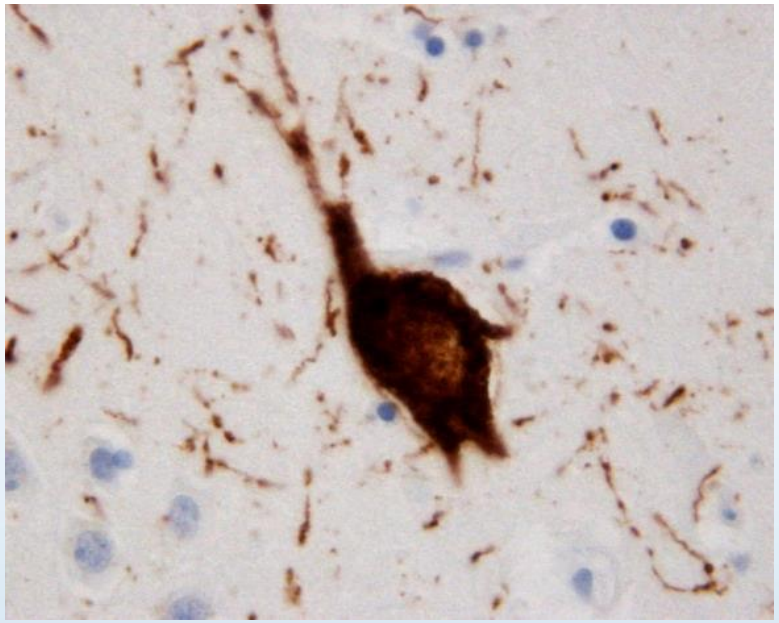
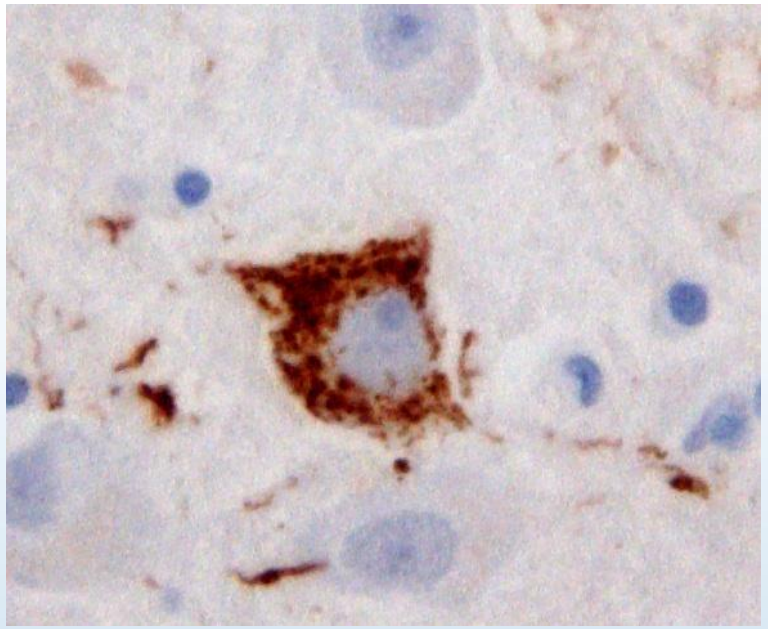
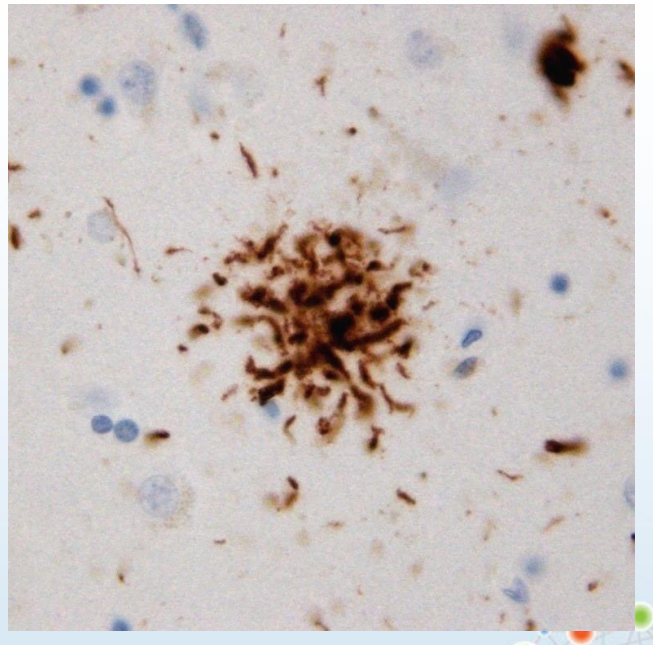
Progressive supranuclear palsy (PSP)
Neuropathology: 4R tau



Neurofibrillary tangle



Pretangle



Tufted astrocyte

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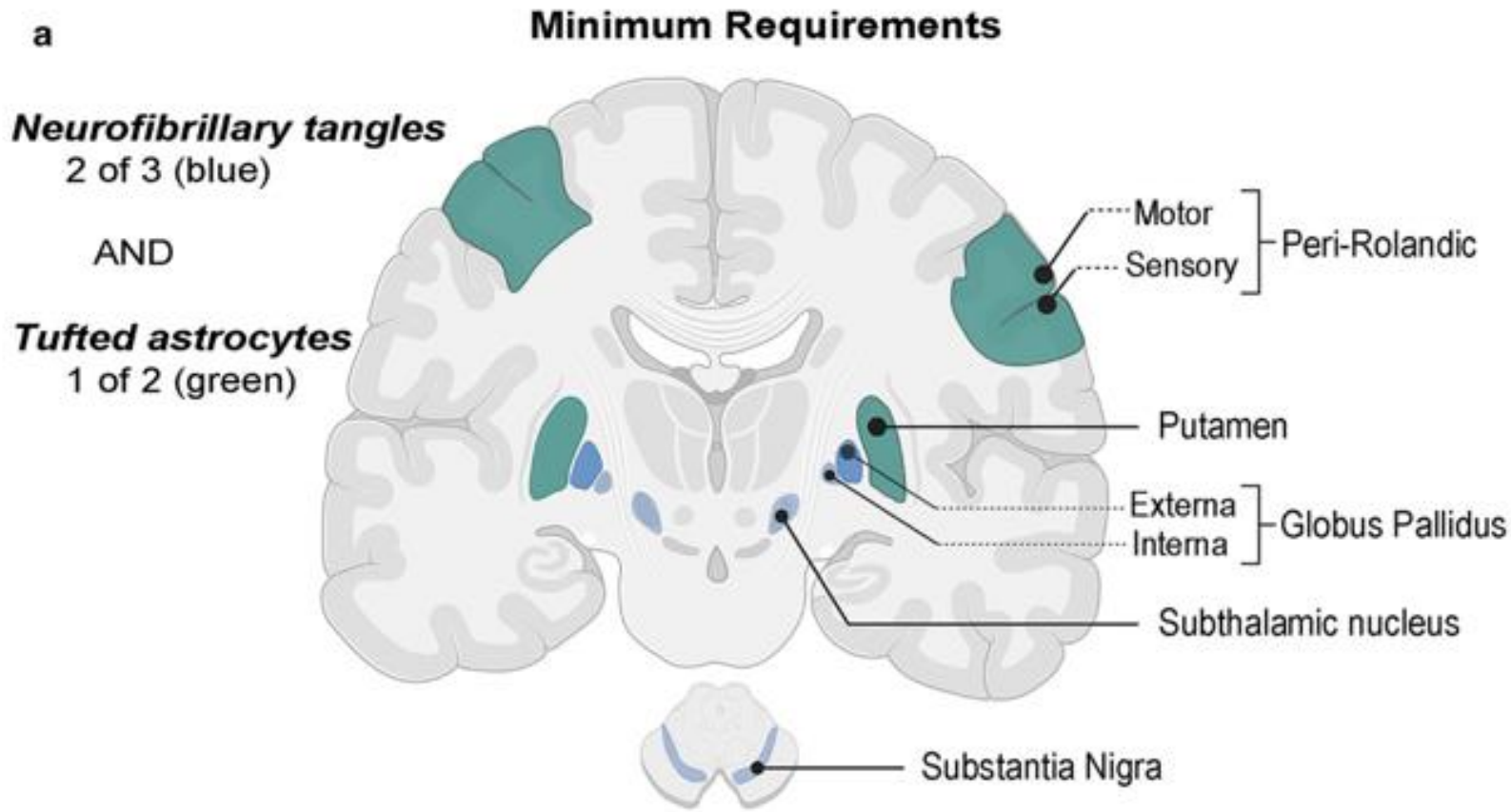
PSP revised neuropathologic criteria (2022)



Acta Neuropathologica
https://doi.org/10.1007/s00401-022-02479-4

ORIGINAL PAPER

Rainwater Charitable Foundation criteria for the neuropathologic diagnosis progressive supranuclear palsy

Shanu F. Roemer[1] · Lea T. Grinberg[2,3,4] · John F. Crary[5] · William W. Seeley[2,3] · Ann C. McKee[6] · Gabor G. Kovacs[7,8] · Thomas G. Beach[9] · Charles Duyckaerts[10] · Isidro A. Ferrer[11] · Ellen Gelpi[12] · Edward B. Lee[13] · Tamas Revesz[14] · Charles L. White III[15] · Mari Yoshida[16] · Felipe L. Pereira[2] · Kristen Whitney[5] · Nikhil B. Ghayal[1] · Dennis W. Dickson[1]

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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

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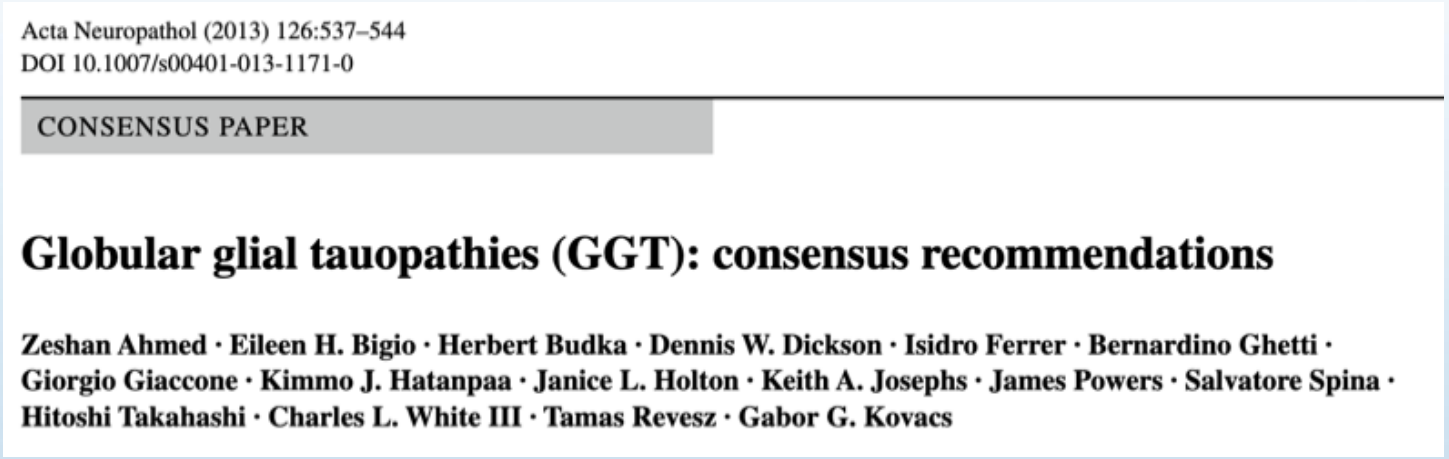
Globular glial tauopathy (GGT)
Neuropathology

- Diagnostic criteria
  - Globular cytoplasmic inclusions in oligodendroglia and astrocytes
  - Coiled bodies in oligodendroglia
- Tau isoform: 4R



Acta Neuropathol (2013) 126:537–544
DOI 10.1007/s00401-013-1171-0

CONSENSUS PAPER

Globular glial tauopathies (GGT): consensus recommendations

Zeshan Ahmed · Eileen H. Bigio · Herbert Budka · Dennis W. Dickson · Isidro Ferrer · Bernardino Ghetti · Giorgio Giaccone · Kimmo J. Hatanpaa · Janice L. Holton · Keith A. Josephs · James Powers · Salvatore Spina · Hitoshi Takahashi · Charles L. White III · Tamas Revesz · Gabor G. Kovacs

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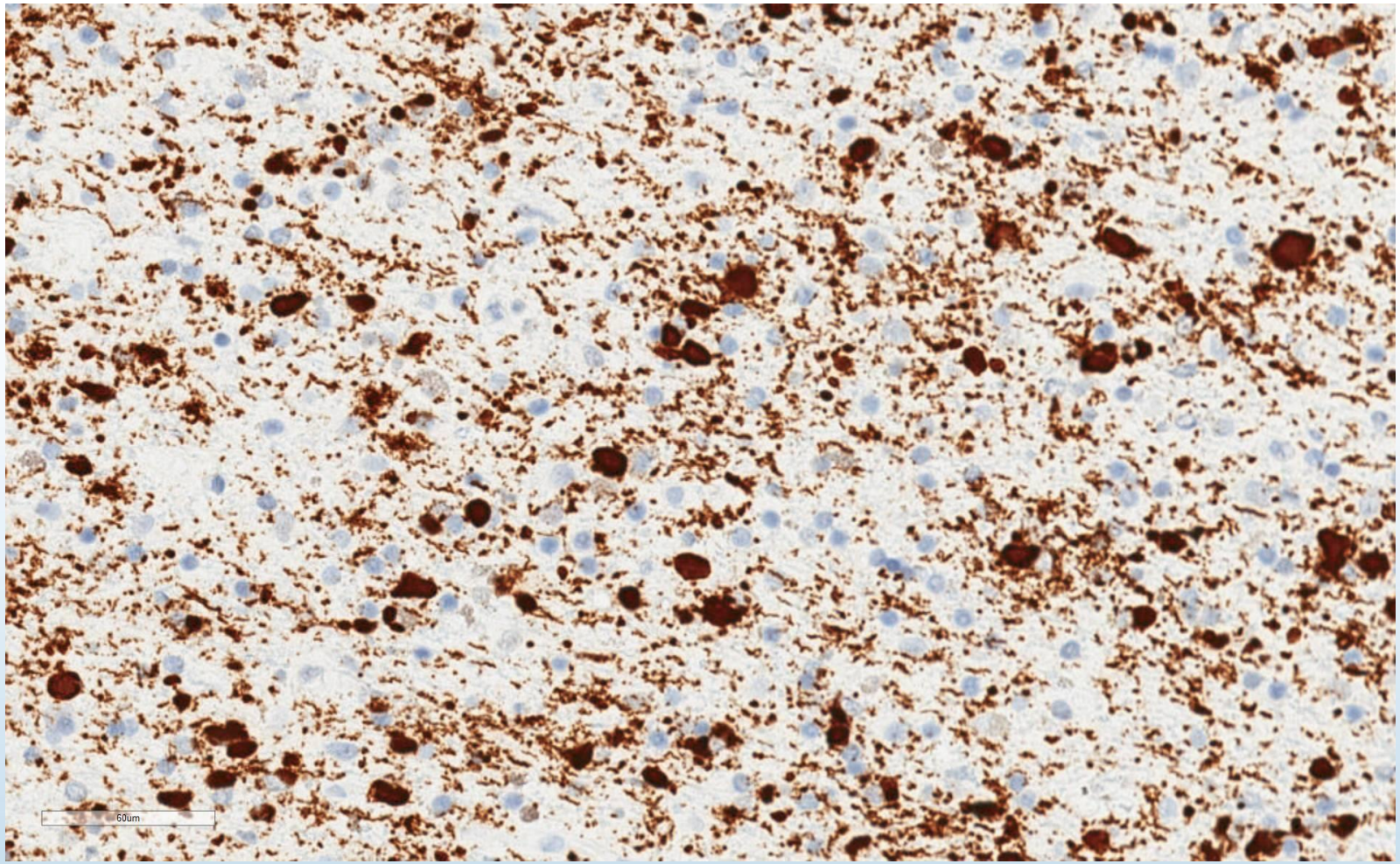
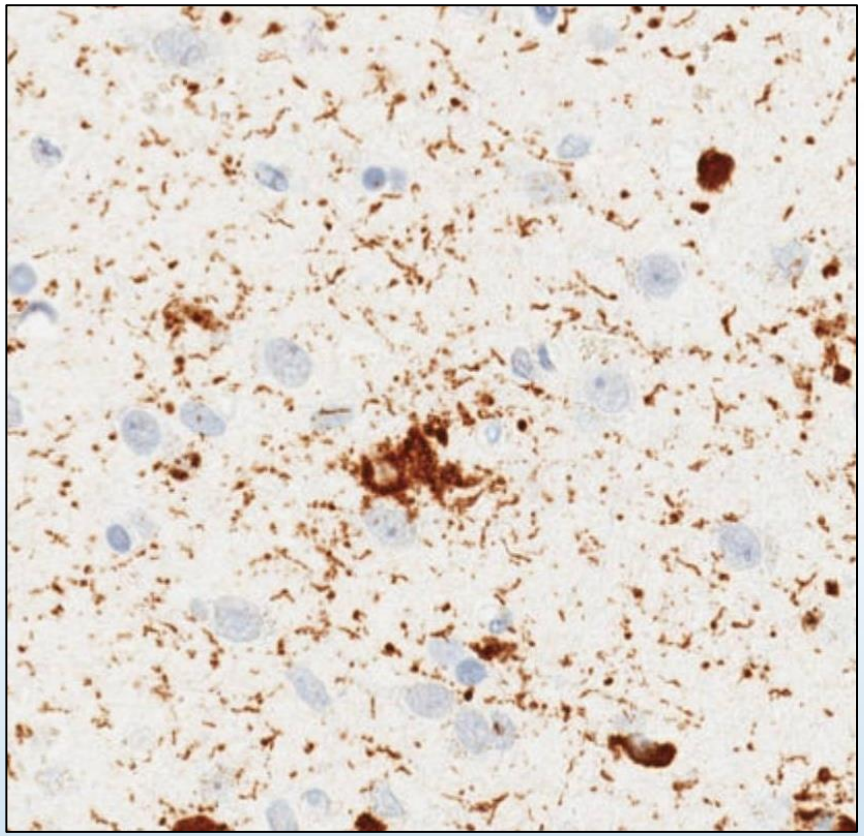
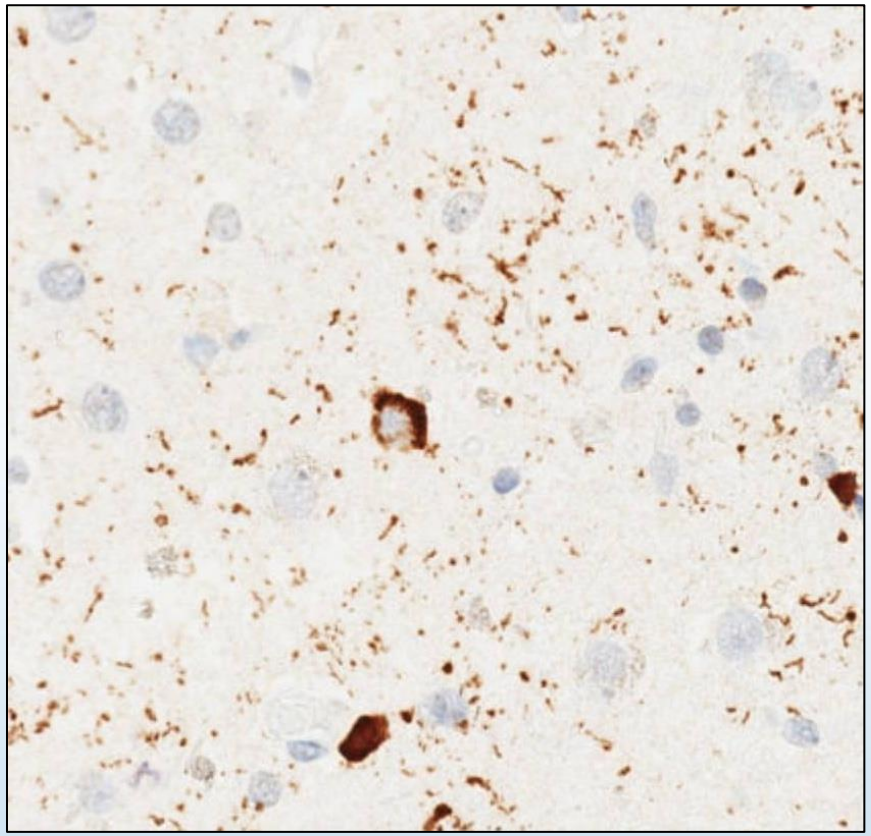
Globular glial tauopathy (GGT)
Neuropathology



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

AANP

Virtual slide

Thank you!

Q & A