Contribution of neuropathology to the diagnosis of dementias

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Disclosure slide

- Nothing to disclose
- No conflict of interest

Neuropathology and dementia

- Neurodegenerative disorders
- Vascular disease
- Inflammatory and infectious conditions
- Toxic-metabolic causes
- Miscellaneous causes: trauma, neoplasia, normal pressure hydrocephalus

Geographical area | **Age group of patients** | **Focus of the neurology department/outpatient clinic**

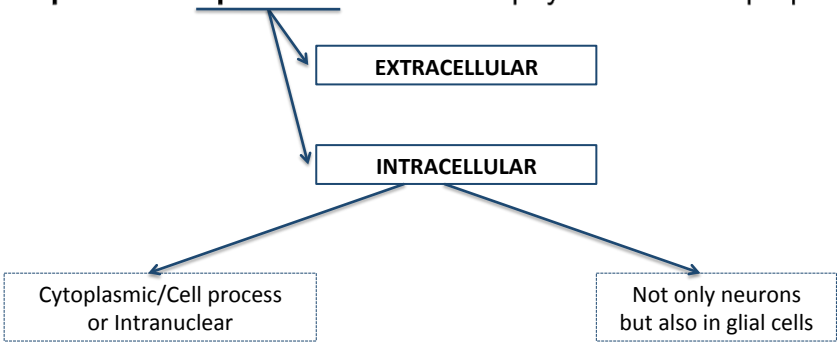
Learning objectives

1. Definition of neurodegenerative diseases
2. Understanding the concepts of classification of neurodegenerative diseases
3. Neuropathological features of major disease-entities
4. Clinicopathological correlation
5. The concept of concomitant pathologies

1

Definition of neurodegenerative diseases

- Neurodegenerative disorders are characterised by regionally distinct neuronal loss and astrogliosis, ***and***
- **Deposition of proteins** with altered physicochemical properties



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2

Classification

Clinical

Anatomical predominance of neuronal degeneration

Predominant protein

Localisation in the CNS: intra-, extracellular, subcellular and cell-type specific differences

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2

Clinical presentations

- Alzheimer-type dementia
- Frontotemporal dementia (FTD)
- Dementia/FTD associated with movement disorder
- Rapidly progressive dementia

2

Clinical presentations Anatomical predominance

Alzheimer type dementia
Entorhinal Cx-Hippocampus-Medial temporal lobe-Neocortex

- **Behavioral variant of FTD (bvFTD)**
  → Prefrontal and anterior temporal regions atrophic
- **Semantic dementia (SD)**
  → Temporal regions atrophic
- **Progressive non-fluent aphasia (PNFA)**
  → Dominant frontotemporal region atrophic
- **Logopenic progressive aphasia (LPA)**
- **FTD and corticobasal syndrome (CBS)**
- **FTD and progressive supranuclear palsy (PSP)**
- **FTD and parkinsonism**
- **FTD and motor neuron disease (MND)**

  → Fronto-temporal + Subcortical regions

FTD (clinical) → **FTLD (macroscopy/MRI)**

Rapid dementia-Prion disease
Neocortex + Subcortical regions (Hippocampus spared)

2

Predominant proteins

Intracellular

TDP-43 | Tau | A-Synuclein | FUS/FET

Localisation of immunoreactivity with relevance for the neuropathological diagnosis

Amyloid-beta | Prion protein

Extracellular

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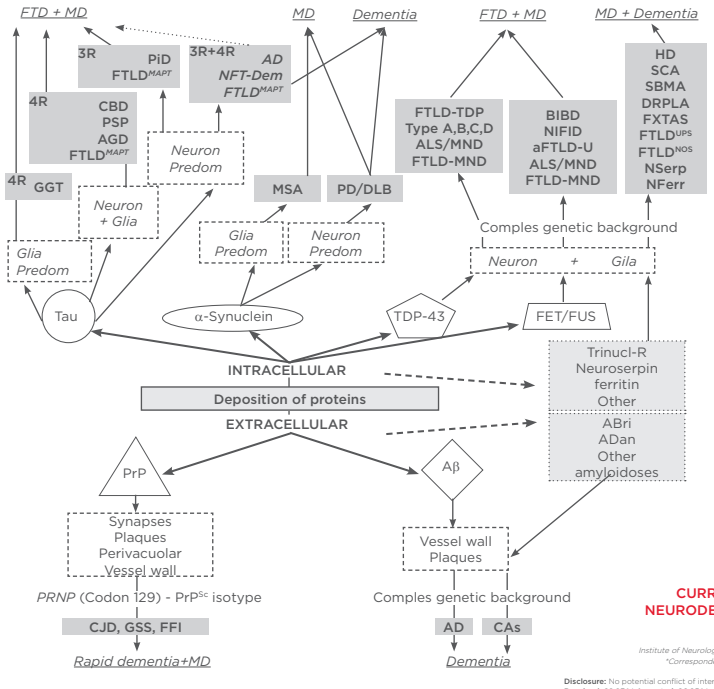

Figure 1: Algorithm for the classification of sporadic neurodegenerative disorders.

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3.1

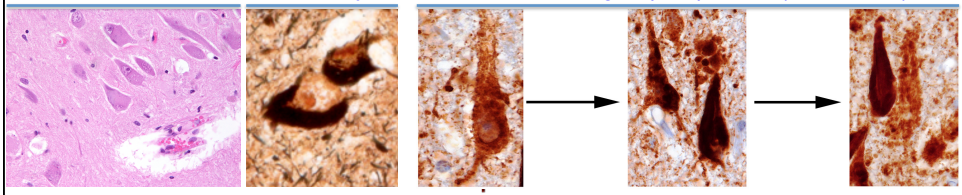
Definition of Alzheimer`s disease

- Neuronal/Synaptic loss in anatomical areas that are important for memory and cognition

+

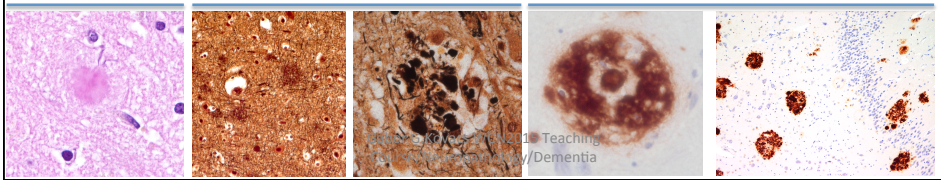
- Neurofibrillary degeneration (intracellular-tau protein)

Hematoxlin-Eosin *Bielschowsky silver* *Immunostaining for phospho-Tau ("maturation")*



"Senile plaques" (beta-amyloid protein)

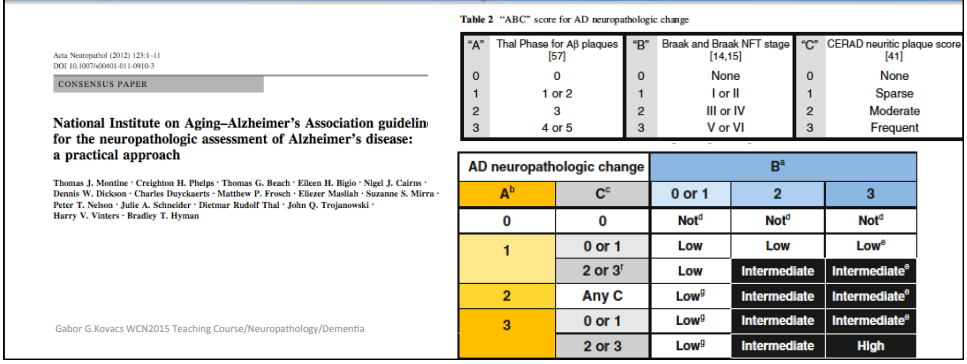
Hematoxlin-Eosin *Bielschowsky silver* *Immunostaining for A-beta*



3.1

Neuropathological diagnosis of Alzheimer`s disease

Semiquantitative score of "neuritic plaques" (silver staining)-CERAD criteria
+
Immunostaining for A-beta: phases of plaque deposition (Thal et al.)
+
Stages of neurofibrillary degeneration (Braak & Braak stages)



Acta Neuropathol (2012) 123:1–11
DOI 10.1007/s00401-011-0910-3

CONSENSUS PAPER

National Institute on Aging–Alzheimer's Association guidelin 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

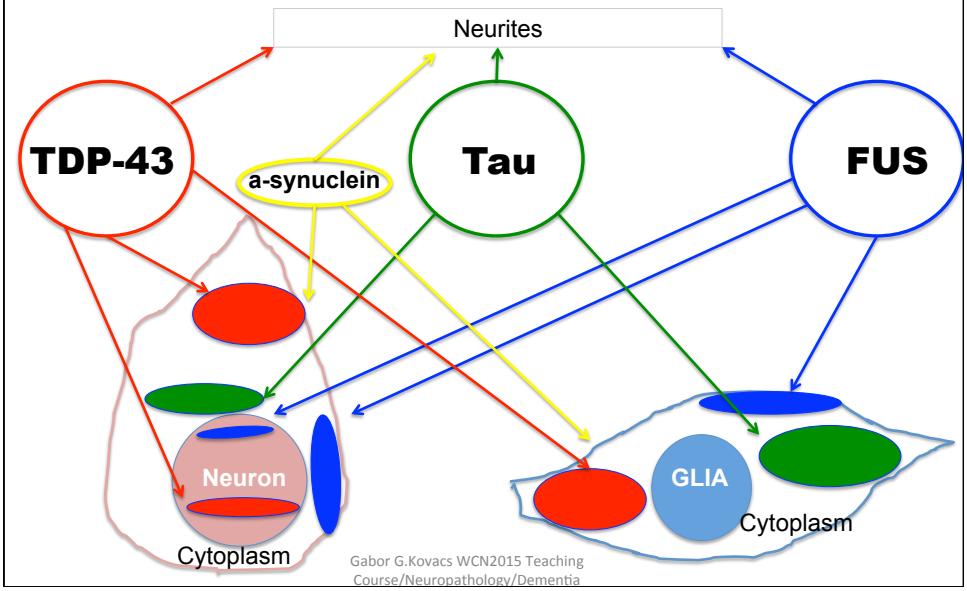
Table 2 "ABC" score for AD neuropathologic change

"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

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

3.2

Neuropathology of FTLD: Involved Proteins and cell types



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Tau

Neuropathological phenotypes: Tauopathies

- Pick`s disease (FLTD-Tau with Pick bodies)
- Progressive supranuclear palsy
- Corticobasal degeneration
- Globular glial tauopathies
- FTLD with MAPT mutations

- *Argyrophilic grain disease*
- *NFT dementia*

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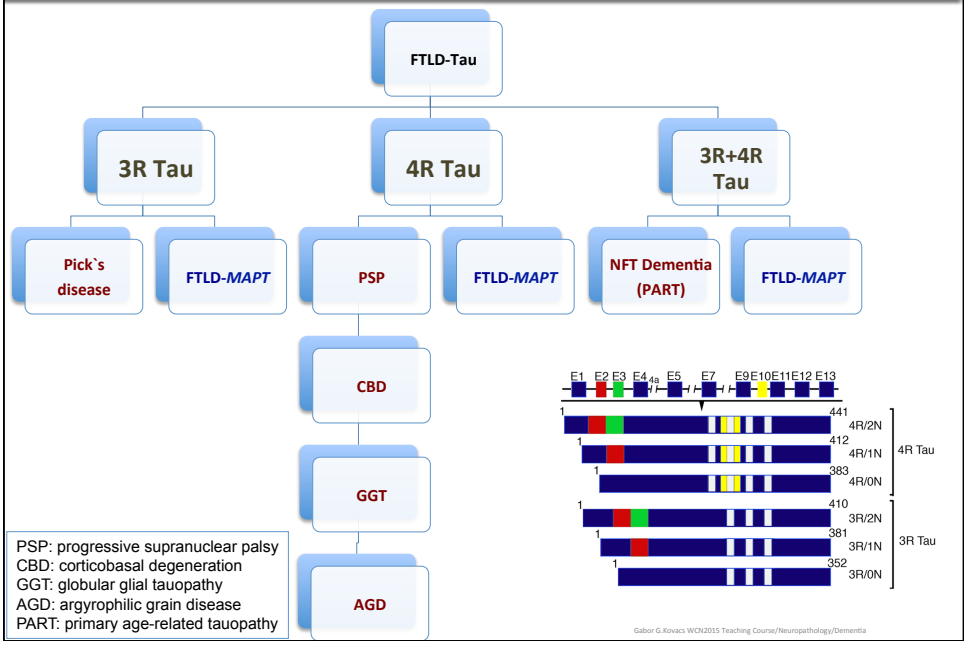
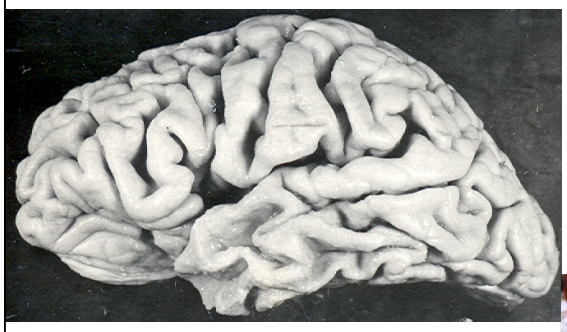
Tau

Molecular classification of Tauopathies



Tau

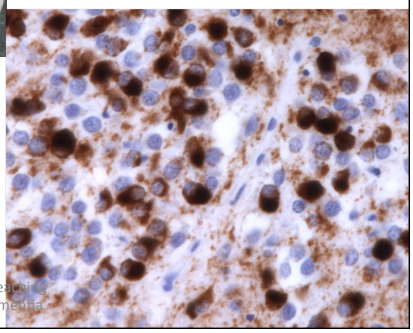
Pick`s Disease: Summary



Neuronal predominant tau pathology

Frontotemporal cortical and hippocampus involvement

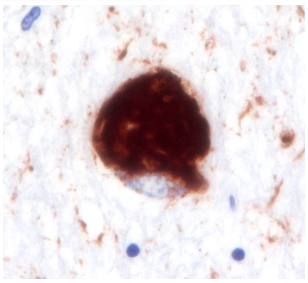
3R tauopathy

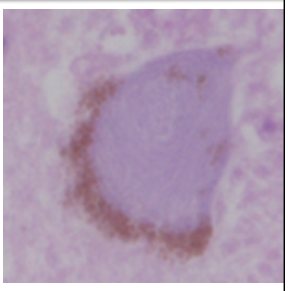


PSP: neuropathology

Neuronal lesions

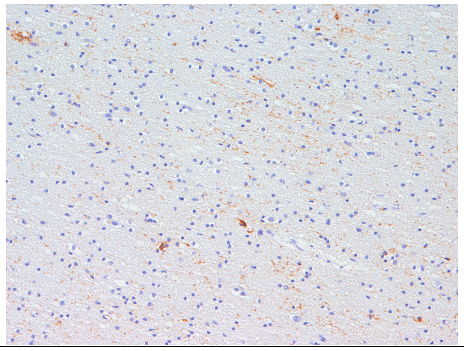
Globose neurofibrillary tangle





Threads

Cortex
&
White matter

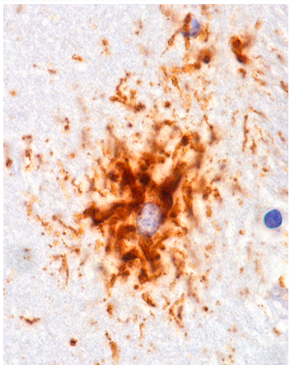


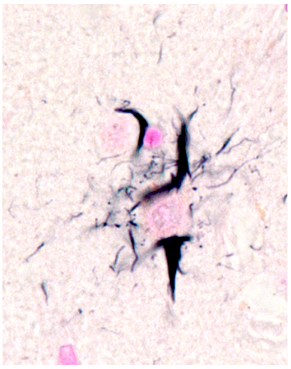
PSP: neuropathology

Glial immunoreactivity

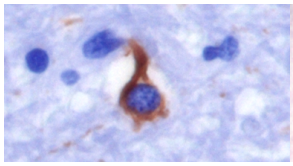
Astrocyte

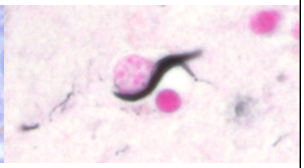
TUFTED ASTROCYTE





Oligodendroglia
COILED BODY

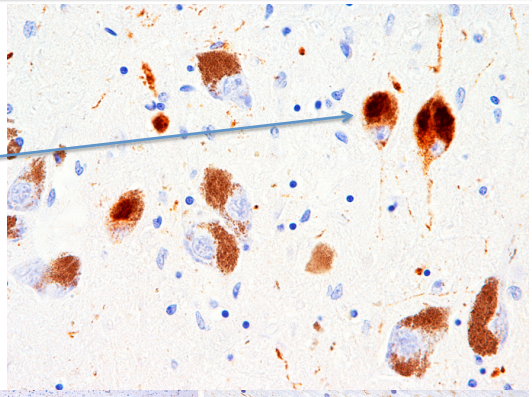




CBD: neuropathology

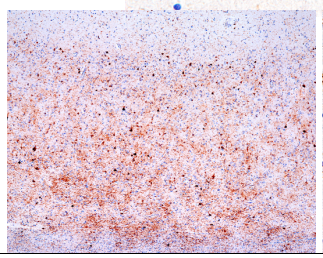
Neuronal lesions

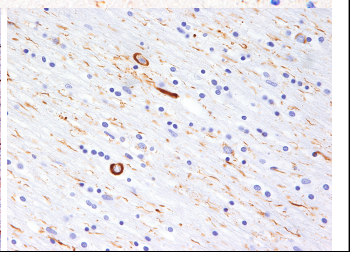
Small spherical inclusions
(„CBD bodies“)
&
Diffuse granular cytoplasmic
Tau immunoreactivity



Threads

Cortex
White matter

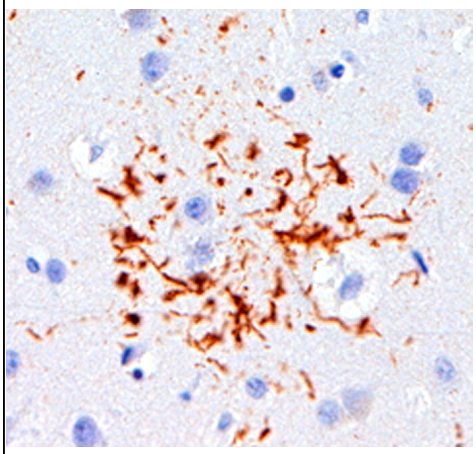


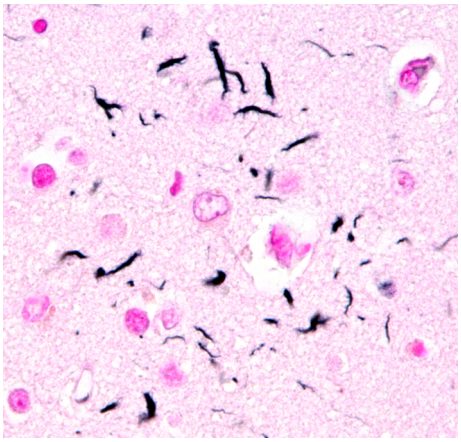


CBD: neuropathology

Glial immunoreactivity

Astrocyte: ASTROCYTIC PLAQUE





Tau

Globular Glial Tauopathies: Summary

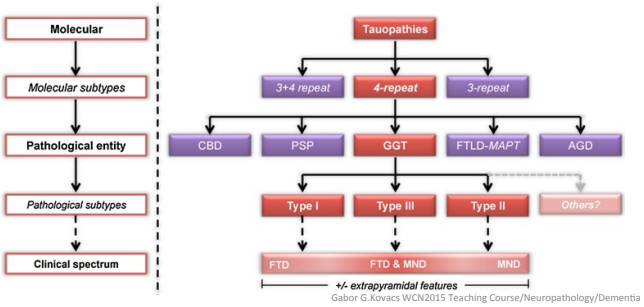
- Recent studies have highlighted a group of 4-repeat (4R) tauopathies that are characterised neuropathologically by widespread, globular glial inclusions (GGIs).
- These cases are associated with a range of clinical presentations, which correlate with the severity and distribution of underlying tau pathology and neurodegeneration.
- Significant degeneration of the white matter is a feature of all GGT subtypes.
- Three (I-III) subtypes are recognized

Acta Neuropathol
DOI 10.1007/s00401-013-1171-0

CONSENSUS PAPER

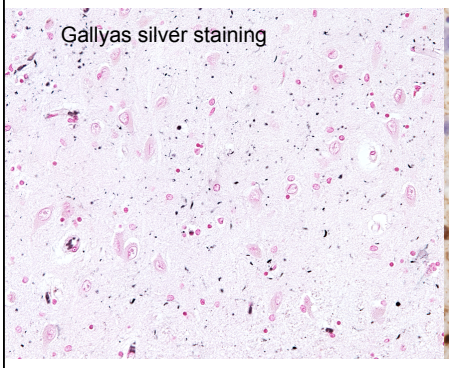
Globular glial tauopathies (GGT): consensus recommendations

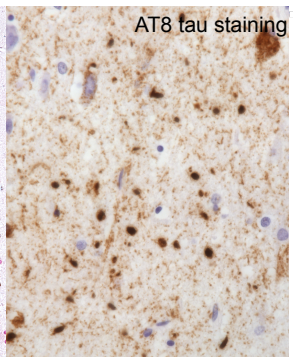
Zeshan Ahmed · Eileen H. Bigio · Herbert Budka · Dennis W. Dickson · Isidro Ferrer · Bernardino Ghetti · Giorgio Giaccone · Kimmo J. Hatanpaa · Janice L. Holton · Keith A. Josephs · James Powers · Salvatore Spina · Hitoshi Takahashi · Charles L. White III · Tamas Revesz · Gabor G. Kovacs

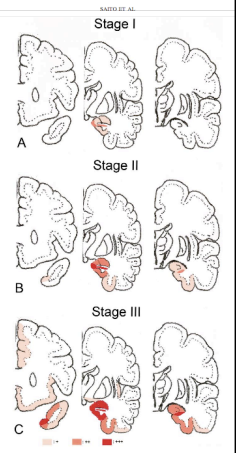


Tau

Argyrophilic Grain Disease







More neuronal and less glial tau pathology

Limbic system involvement

4R tauopathy

Saito et al. JNEN 2004; 63: 911-918

Tau

PART/NFT-dementia

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

"We propose a new term, "primary age-related tauopathy" (PART), to describe a **pathologic continuum** ranging from focally distributed neurofibrillary tangles (NFTs) observed in **cognitively normal aged** individuals, through the pathology observed in **persons with dementing illnesses** that have been referred to as "tangle-predominant senile dementia" (TPSD), "tangle-only dementia", "preferential development of NFT without senile plaques", and "senile dementia of the neurofibrillary tangle type" (SD-NFT), among other names."

Feature	PART (NFT dementia)	Alzheimer disease
ApoE	e3 or e2 very rare e4	frequent e4
Braak Stage (NFT)	Only up to IV	V-VI
Amyloid plaques	Virtually absent	Frequent
Amyloid angiopathy	Rare	Frequent
Glial tau pathology	Rather frequent	Rare

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TDP -43

Neuropathological phenotypes: TDP-43

Classification according to:
- Sampathu et al. (1,2,3)
- Mackenzie et al. (1,2,3,4)
- Consensus (A,B,C,D)

Acta Neuropathol (2011) 122:111–113
DOI 10.1007/s00401-011-0845-8

CONSENSUS LETTER

A harmonized classification system for FTLD-TDP pathology

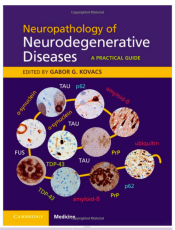
Ian R. A. Mackenzie · Manuela Neumann · Atik Baborie · Deepak M. Sampathu · Daniel Du Plessis · Evelyn Jaros · Robert H. Perry · John Q. Trojanowski · David M. A. Mann · Virginia M. Y. Lee

Table 1 Proposed new classification system for FTLD-TDP pathology, compared with existing systems

New system	Mackenzie et al. [7]	Sampathu et al. [11]	Cortical pathology	Common phenotype	Associated genetic defects
Type A	Type 1	Type 3	Many NCI Many short DN Predominantly layer 2	bvFTD PNFA	*GRN* mutations
Type B	Type 3	Type 2	Moderate NCI Few DN All layers	bvFTD MND with FTD	Linkage to chromosome 9p
Type C	Type 2	Type 1	Many long DN Few NCI Predominantly layer 2	SD bvFTD	
Type D	Type 4[a]	Type 4[a]	Many short DN Many lentiform NII Few NCI All layers	Familial IBMPFD	*VCP* mutations

bvFTD behavioural variant frontotemporal dementia, *DN* dystrophic neurites, *GRN* progranulin gene, *IBMPFD* inclusion body myopathy with Paget's disease of bone and frontotemporal dementia, *MND* motor neuron disease, *NCI* neuronal cytoplasmic inclusions, *NII* neuronal intranuclear inclusions, *PNFA* progressive non-fluent aphasia, *SD* semantic dementia, *VCP* valosin-containing protein gene

[a] Described subsequently by Forman et al. [4]



Molecular pathology	Subtype	Gene
FTLD-Tau	PiD PSP CBD GGT AGD* NFT-dementia* FTLD with *MAPT* mutation	*MAPT*
FTLD-TDP	Type A Type B Type C Type D ALS-FTLD-TDP	*GRN* *C9orf72* *VCP* *TARDBP*[b]
FTLD-FUS	aFTLD-U* NIFID* BIBD* ALS-FTLD-FUS	*FUS*
FTLD-UPS	FTD-3	*CHMP2B*
FTLD-NOS	DLDH	

Central element in the classification is the recognition of neuritic **(DN)**, neuronal cytoplasmic (**NCI**) and neuronal nuclear inclusions (**NNI**) in particular anatomical regions

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FUS

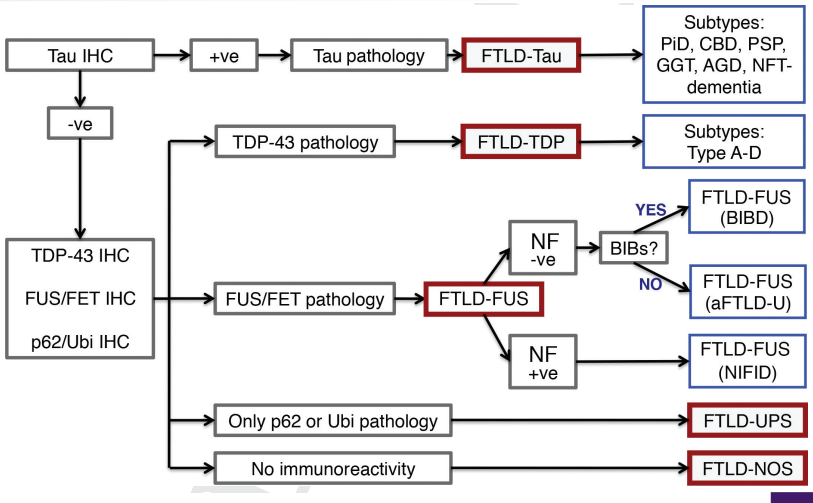
Neuropathological phenotypes: FUS proteinopathies

- Atypical FTLD-U
- Basophilic inclusion body disease
- Neuronal intermediate filament disease (*alpha-internexin and neuronal intermediate filament* positive ALSO)

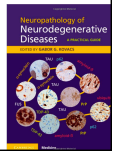
These are negative for tau, a-synuclein, TDP-43

Clinical: bvFTD and extrapyramidal symptoms (+MND)

FTLD: Diagnostic algorithm



aFTLD-U, atypical frontotemporal lobar degeneration with ubiquitinated inclusions; AGD, argyrophilic grain disease; BIBD, basophilic inclusion body disease; BIBs, basophilic inclusion bodies; CBD, corticobasal degeneration; FET (FUS, EWS and TAF15 family of proteins); GGT, globular glial tauopathy; IHC, immunohistochemistry; NIFID, neuronal intermediate filament inclusion disease; NF, neurofilament (includes neuronal intermediate filaments, intermediate filament protein and also α-internexin); NFT, neurofibrillary tangles; NOS, not otherwise specified; PiD, Pick's disease; PSP, progressive supranuclear palsy; TDP, transactive response-binding protein; UPS, ubiquitin–proteasome system.



Clinical-molecular-pathological correlations

Acta Neuropathol (2011) 122:137–153
DOI 10.1007/s00401-011-0839-6

REVIEW

Neuropathological background of phenotypical variability in frontotemporal dementia

Keith A. Josephs · John R. Hodges · Julie S. Snowden · Ian R. Mackenzie · Manuela Neumann · David M. Mann · Dennis W. Dickson

frontiers in AGING NEUROSCIENCE
REVIEW ARTICLE
published: 19 August 2014
doi: 10.3389/fnagi.2014.00204

Therapeutic and diagnostic challenges for frontotemporal dementia

Simon D'Alton and Jada Lewis*
Department of Neuroscience, Center for Translational Research in Neurodegenerative Disease, College of Medicine, University of Florida, Gainesville, FL, USA

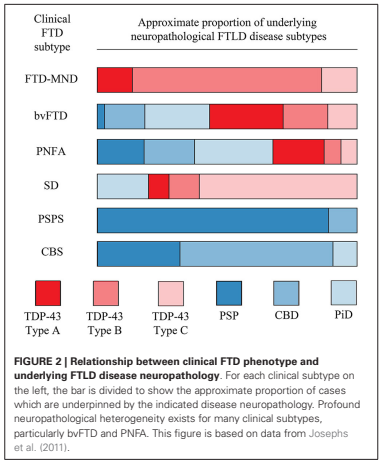


FIGURE 2 | Relationship between clinical FTD phenotype and underlying FTLD disease neuropathology. For each clinical subtype on the left, the bar is divided to show the approximate proportion of cases which are underpinned by the indicated disease neuropathology. Profound neuropathological heterogeneity exists for many clinical subtypes, particularly bvFTD and PNFA. This figure is based on data from Josephs et al. (2011).

FTLD-synuclein

MSA may present clinically and pathologically as a frontotemporal lobar degeneration.

Acta Neuropathol (2015) 130:93–105
DOI 10.1007/s00401-015-1442-z

ORIGINAL PAPER

Atypical multiple system atrophy is a new subtype of frontotemporal lobar degeneration: frontotemporal lobar degeneration associated with α-synuclein

Naoya Aoki[1] · Philip J. Boyer[2] · Cheryl Lund[3] · Wen-Lang Lin[1] · Shunsuke Koga[1] · Owen A. Ross[1] · Myron Weiner[4] · Anne Lipton[4] · James M. Powers[5] · Charles L. White III[6] · Dennis W. Dickson[1]

Acta Neuropathol (2015) 130:299–301
DOI 10.1007/s00401-015-1455-7

CORRESPONDENCE

Screening for α-synuclein immunoreactive neuronal inclusions in the hippocampus allows identification of atypical MSA (FTLD-synuclein)

Zdenek Rohan[1,2] · Jasmin Rahimi[3] · Serge Weis[4] · Istvan Kapas[2] · Eduard Auff[4] · Nenad Mitrovic[2] · Pawel P. Liberski[5] · Beata Sikorska[5] · Radoslav Matej[2,3,6] · Gabor G. Kovacs[3]

Classical Papp-Lantos bodies (glial cytoplasmic inclusions)

+ neuronal a-synuclein pathology in the FT lobe and hippocampus!

Dementia with Lewy bodies

TERM	Remark
Lewy body disease	Neuropathological term: includes all diseases
Diffuse/transitional/brainstem-predominant Lewy body disease	Neuropathological term: describes the distribution
Dementia with Lewy bodies	Clinical term: the neuropathology associated with it is mostly Lewy body disease
AD with amygdala Lewy bodies	Diagnostic category
AD with incidental Lewy bodies	Clinical and neuropathological features
Parkinson disease dementia	Clinical term; There is no gold standard for the neuropathological diagnosis of DLB or Parkinson`s disease dementia

Modified from: Lowe J and Kalaria R. Dementia; In: Love S, Budka H, Ironside JW, Perry A: Greenfield`s Neuropathology, 9th Edition, CRC Press

Classification of Lewy body disease

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

None	No LBs or related changes in IHC for α-synuclein
Brainstem-predominant	LBs in medulla, pons, or midbrain
Limbic (Transitional)	LBs in cingulate or entorhinal cortices, usually with brainstem involvement
Neocortical (Diffuse)	LBs in frontal, temporal, or parietal cortices usually with involvement of brainstem and limbic sites, which may include amygdala
Amygdala-predominant	LBs in amygdala with paucity of LBs in the above regions

Dementia with Lewy bodies

McKeith et al. Protocol-2005

Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium

I. G. McKeith, D. W. Dickson, J. Lowe, M. Emre, J. T. O'Brien, H. Feldman, J. Cummings, J. E. Duda, C. Lippa, E. K. Perry, D. Aarsland, H. Arai, C. G. Ballard, B. Boeve, D. J. Burn, D. Costa, T. Del Ser, B. Dubois, D. Galasko, S. Gauthier, C. G. Goetz, E. Gomez-Tortosa, G. Halliday, L. A. Hansen, J. Hardy, T. Iwatsubo, R. N. Kalaria, D. Kaufer, R. A. Kenny, A. Korczyn, K. Kosaka, V.M.Y. Lee, A. Lees, I. Litvan, E. Londos, O. L. Lopez, S. Minoshima, Y. Mizuno, J. A. Molina, E. B. Mukaetova-Ladinska, F. Pasquier, R. H. Perry, J. B. Schulz, J. Q. Trojanowski, M. Yamada and for the Consortium on DLB

Neurology 2005;65;1863-1872; originally published online Oct 19, 2005;
DOI: 10.1212/01.wnl.0000187889.17253.b1

Semiquantitative rating of Lewy body pathology

Table 2 *Assignment of Lewy body type based upon pattern of Lewy-related pathology in brainstem, limbic, and neocortical regions*

Lewy body type pathology	Brainstem regions			Basal forebrain/limbic regions				Neocortical regions		
	IX-X	LC	SN	nbM	Amygdala	Transentorhinal	Cingulate	Temporal	Frontal	Parietal
Brainstem-predominant	1-3	1-3	1-3	0-2	0-2	0-1	0-1	0	0	0
Limbic (transitional)	1-3	1-3	1-3	2-3	2-3	1-3	1-3	0-2	0-1	0
Diffuse neocortical	1-3	1-3	1-3	2-3	3-4	2-4	2-4	2-3	1-3	0-2

Assessment of the likelihood

Table 3 *Assessment of the likelihood that the pathologic findings are associated with a DLB clinical syndrome*

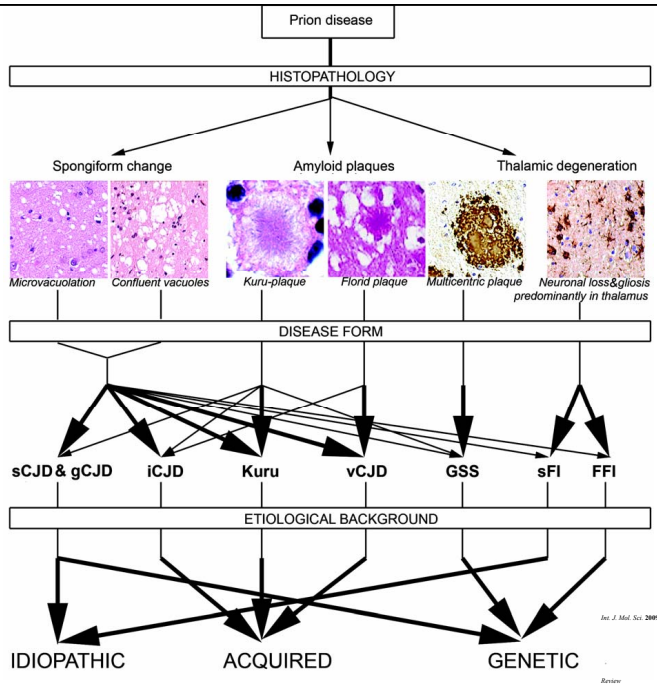
	Alzheimer type pathology		
	NIA-Reagan Low (Braak stage 0–II)	NIA-Reagan Intermediate (Braak stage III–IV)	NIA-Reagan High (Braak stage V–VI)
Lewy body type pathology			
Brainstem-predominant	Low	Low	Low
Limbic (transitional)	High	Intermediate	Low
Diffuse neocortical	High	High	Intermediate

3.4

Human prion diseases

Name	Abbreviation	Etiology	Remark
Sporadic Creutzfeldt-Jakob disease	sCJD	Idiopathic	Molecular subtypes
Sporadic fatal insomnia	sFI	Idiopathic	Subtype of sCJD
Variably Protease-Sensitive Prionopathy	PsPsen	Idiopathic	Novel form
Variant Creutzfeldt-Jakob disease	vCJD	Acquired	Associated with BSE
Iatrogenic Creutzfeldt-Jakob disease	iCJD	Acquired	Associated with:
			Hu GH
			Hu GonatrophinH
			Dura transplant
			Neurosurgery
			Cornea transplant
			Deep electrodes
Kuru	Kuru	Acquired	Associated with cannibalism
Genetic Creutzfeldt-Jakob disease	gCJD	*PRNP* mutation	> 30 mutations
Fatal familial Insomnia	FFI	*PRNP* mutation	1 mutation
Gerstmann-Sträussler-Scheinker disease	GSS	*PRNP* mutation	> 10 mutations
			Amyloidosis
PrP cerebral amyloid angiopathy	PrP-CAA	*PRNP* mutation	Vascular amyloid

I.Quadrio, A. Perret-Liaudet , G. G. Kovacs. Molecular diagnosis of human prion disease. **Expert Opin Med Diagn. 2011:5:291-306**



Int. J. Mol. Sci. **2009**, *10*, 976-999; doi:10.3390/ijms10030976
OPEN ACCESS
International Journal of Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms
Review

Molecular Pathology of Human Prion Diseases

Gabor G. Kovacs and Herbert Budka *

Gabor G.Kovacs WCN2015 Teaching Course/Neuropathology/Dementia

Sporadic CJD: clinicopathological / molecular subtypes

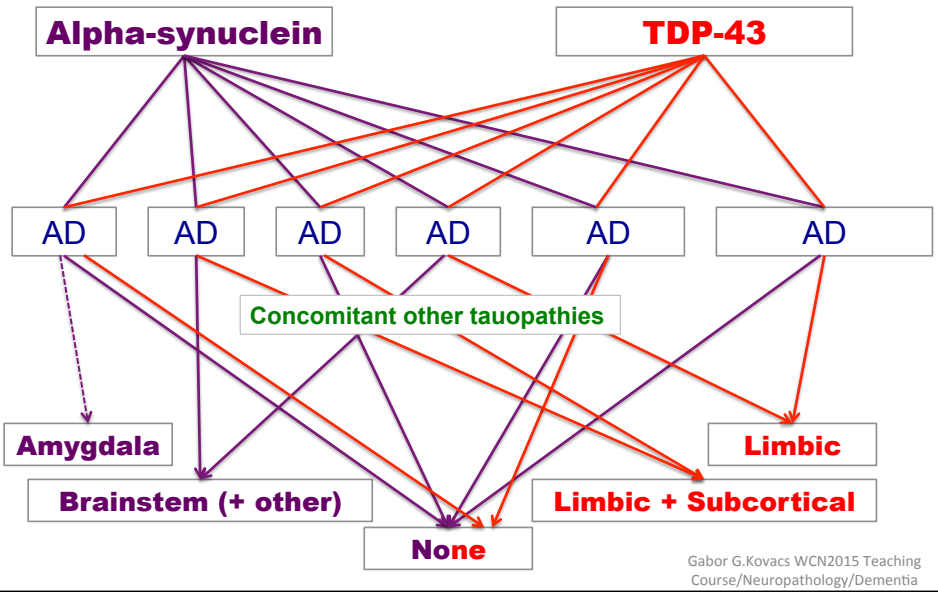
Feature/Subtype	MM-1	MV-1	MM/MV-2 C	MM-2 T	MV-2K	VV-1	VV-2
Clinical features	Rapidly progressive dementia, myoclonus, ataxia,and visual impairment		Cognitive impairment, myoclonus, and pyramidal signs	Insomnia, psychomotor hyperactivity, ataxia and motor signs	Ataxia and dementia long clinical duration	Progressive dementia with myoclonus and pyramidal signs	Ataxia at onset, dementia in later stage
Typical duration	4 (1-24) / 3,8		20 (12-36)	15,5 (8-24)	15,8 (5-48)	15,3 (14-16)	6,3 (3-18)
Age at Onset	70 (48-86)		67,8 (61-75)	52,3 (36-71)	65,4 (48-81)	39,3 (24-49)	64,5 (45-83)
14-3-3 sensitivity	91	86	61	/	71	90	95
	92	91	78	/	65	100	90
	94	100	70	/	57	100	84
MRI: signals in	BG / Cx		Widespread cortical	No typical sign	BG / thalamus	Widespread cortical	BG / thalamus
EEG	PSWCs		no PSWCs	no PSWCs	no PSWCs	no PSWCs	no PSWCs
Topography	Neocortex		Neocortex	Thalamus	Basal ganglia	Neocortex	Basal ganglia
	Basal ganglia			Inferior olives	Thalamus	Basal ganglia	Thalamus
	Cerebellum			(Atrophy)	Cerebellum		Cerebellum
					Neocortex		Cortex deep layers
					Hippocampus		Hippocampus
					Brainstem		Brainstem
Type of vacuoles	Small vacuoles		Large and confluent	Focal small in cortex	Small vacuoles	Medium sized	Small vacuoles
Amyloid plaques	No		No	No	Yes	No	No
PrP IR	Diffuse synaptic		Patchy/perivacuolar	Focal synaptic	Plaque-like	Focal synaptic	Plaque-like
					Perineuronal		Perineuronal
					Focal deposits		Focal deposits

Isabelle Quadrio, Armand Perret-Liaudet A, Gabor G. Kovacs. Molecular diagnosis of human prion disease.
Expert Opin Med Diagn. 2011:5:291-306

Based on the polymorphic codon 129 and Western blot pattern of protease resistant PrP

Gabor G.Kovacs WCN2015 Teaching Course/Neuropathology/Dementia

Alzheimer`s disease is a multi-proteinopathy



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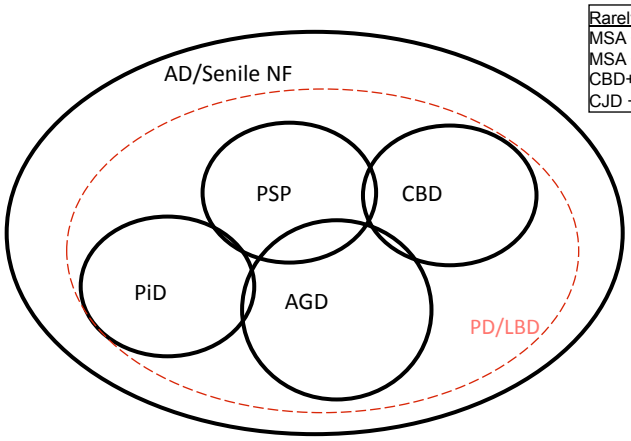
Tauopathy as concomitant pathology



Rarely reported combinations
MSA + AD
MSA + PSP
CBD+ CJD
CJD + PD + AD

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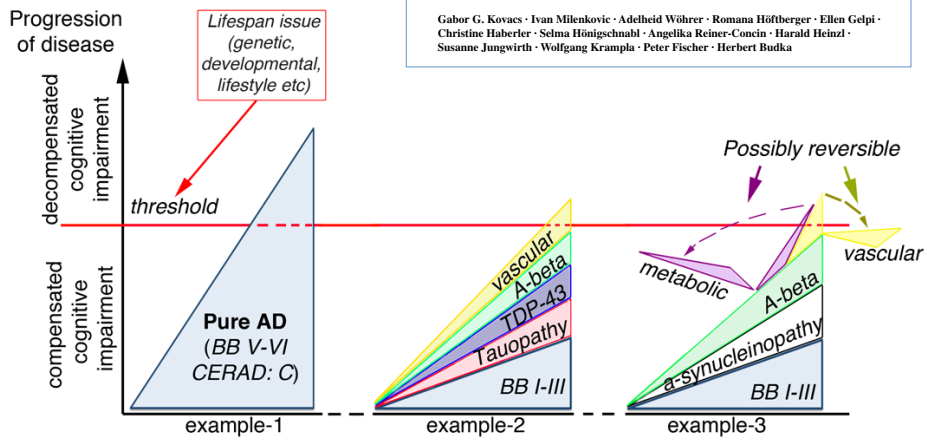
Acta Neuropathol (2013) 126:365–384
DOI 10.1007/s00401-013-1157-y

ORIGINAL PAPER

Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: a community-based autopsy series

Gabor G. Kovacs · Ivan Milenkovic · Adelheid Wöhrer · Romana Höftberger · Ellen Gelpi · Christine Haberler · Selma Hönigschnabl · Angelika Reiner-Concin · Harald Heinzl · Susanne Jungwirth · Wolfgang Krampla · Peter Fischer · Herbert Budka



Better stratification of patients for therapy trials

Gabor G.Kovacs WCN2015 Teaching Course/Neuropathology/Dementia

Recommended literature

- **Protein-based classification:**

Kovacs GG, Botond G, Budka H. Protein coding of neurodegenerative dementias. Acta Neuropathol. 2010 Apr;119(4):389-408.

- **Alzheimer`s disease:**

Montine TJ, et al.; National Institute on Aging; Alzheimer's Association. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol. 2012 Jan;123(1): 1-11

- **PART:**

Crary JF et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol (2014) 128:755–766

- **Tauopathies:**

Kovacs GG: Invited review: Neuropathology of tauopathies: principles and practice. Neuropathol Appl Neurobiol 2015;41:3-23.

- **Synucleinopathies**

Jellinger KA. Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. Mov Disord 2012;27:8-30.

- **Update on FTLD:**

Rosa Rademakers, Manuela Neumann and Ian R. Mackenzie. Advances in understanding the molecular basis of frontotemporal dementia. Nat. Rev. Neurol. 2012: 8, 423–434

- **Prion disease:**

Isabelle Quadrio, Armand Perret-Liaudet A, Gabor G. Kovacs. Molecular diagnosis of human prion disease. Expert Opin Med Diagn. 2011:5:291-306

- **Neuropathological diagnostic approach:**

Kovacs GG, Budka H. Current concepts of neuropathological diagnostics in practice: neurodegenerative diseases. Clin Neuropathol. 2010:29:271-88.