AD and concomitant disease: pathologic perspective

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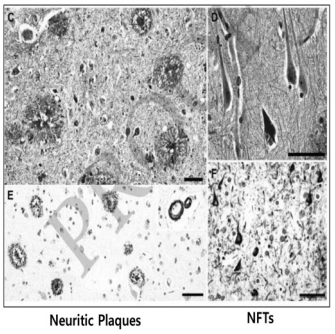
Alzheimer's disease



1. Neuritic Plaque (β-amyloid)
2. Neurofibrillary Tangle (NFT, Tau)

Neuritic Plaques NFTs

Kim et al. 2017

ELSEVIER

Alzheimer's & Dementia

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

Bradley T. Hyman[a], Creighton H. Phelps[b], Thomas G. Beach[c], Eileen H. Bigio[d], Nigel J. Cairns[e,f], Maria C. Carrillo[g], Dennis W. Dickson[h], Charles Duyckaerts[i], Matthew P. Frosch[j], Eliezer Masliah[k,l], Suzanne S. Mirra[m], Peter T. Nelson[n], Julie A. Schneider[o,p,q], Dietmar Rudolf Thal[r], Bill Thies[g], John Q. Trojanowski[s], Harry V. Vinters[t,u], Thomas J. Montine[v,*]

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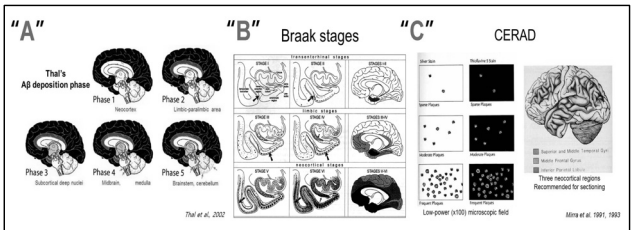
NIA-AA AD neuropathological criteria (ABC score)



"A"	Thal Phase for Aβ deposit	"B"	Braak and Braak NFT stage	"C"	CERAD neuritic plaque score
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[3]		
A[1]	C[2]	0 or 1	2	3
0	0	Not[4]	Not[4]	Not[4]
1	0 or 1	Low	Low	Low[4]
	2 or 3[5]	Low	Intermediate	Intermediate[4]
2	Any C	Low[4]	Intermediate	Intermediate[4]
3	0 or 1	Low[4]	Intermediate	Intermediate[4]
	2 or 3	Low[4]	Intermediate	High

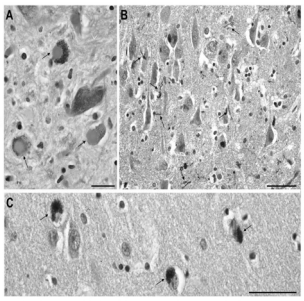
Commonly coexistent diseases

- Lewy body disease (LBD)
- Cerebrovascular disease (CVD) and Vascular brain injury (VBI)
- Hippocampal sclerosis (HS) and TDP-43 inclusions

Hyman et al., 2012

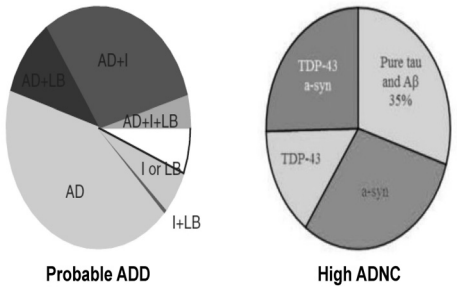
Lewy body disease (LBD)

- Associated with α-synuclein deposits
- Within neuron (Lewy Bodies), and process (Lewy Neurites)
- Underlying pathology of DLB, PDD, PD



Macedo et al., 2007

AD: LBD co-patholgy

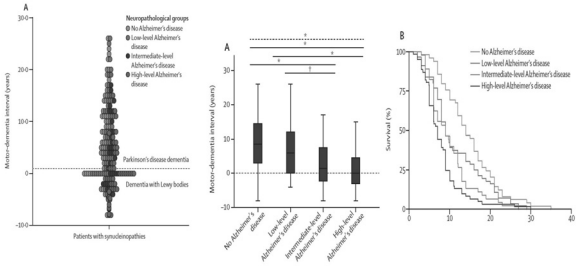


Schneider et al., 2009; Robison et al., 2018

AD: LBD co-patholgy

- ≥ 60% AD cases have LBD (Hamilton, 2000)
  - Amygdala>transitional limbic>neocortical
- Clinical associations (*Chung et al., 2015; Savica et al., 2019*)
  - Male
  - Younger age at onset and at death
  - More behavioral problems
  - Poorer motor performance
- Genetic associations (*Leverenz et al., 2006; Chung et al., 2015*)
  - ≥ 50% *PSEN1, PSEN2* cases have Lewy body pathology
  - Higher ApoE Ɛ4 allele

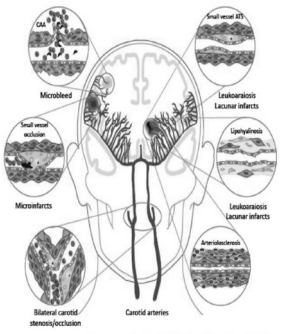
LBD: AD co-pathology



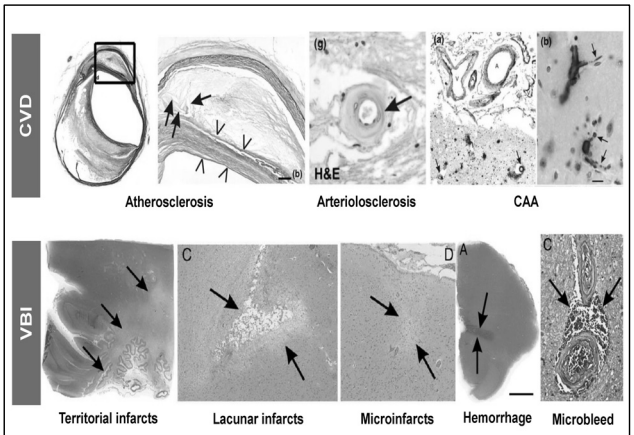
Irwin et al., 2017

CVD and VBI

- CVD
  - Atherosclerosis
  - Arteriolosclerosis (small v. disease)
  - Cerebral amyloid angiopathy
- VBI
  - Infarcts
    - Territorial infarcts
    - Lacunar infarcts
    - Microinfarcts
  - Hemorrhages
    - Visible hemorrhage
    - Microhemorrhage

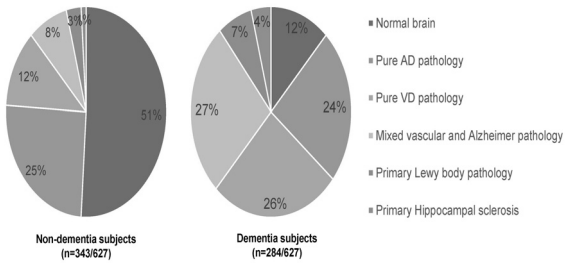


Hyman et al., 2012; Ladecola, 2013



Grinberg & Thal., 2010; Thal et al., 2012

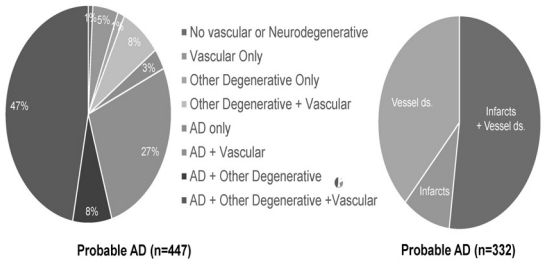
AD: CVD-co pathology



"Concomitant vascular and neurodegenerative pathology double the risk of dementia"

Azarpazhooh et al., 2018

AD: CVD-co pathology



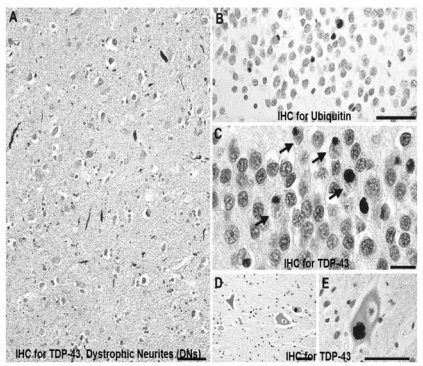
"Cerebrovascular pathology acts synergistically with AD in driving cognitive impairment and dementia, and highly dependent on the type of CVD and the location of lesion"

Kapasi et al., 2017

TDP-43

- Ubiquitously expressed
- Highly conserved RNA- and DNA-binding nuclear protein, exon skipping/translation regulation
- Encoded by the *TARDBP* gene on Chr 1
- In FTLD-U, abnormally phosphorylated, ubiquitinated, and cleaved, resulting in the generation of toxic C-terminal fragments, and nuclear to cytoplasmic translocation
- Clinicopathological spectrum: FTLD-U (FTLD-TDP) pathology, ALS with dementia, classical ALS *(Neuman et al., 2006)*

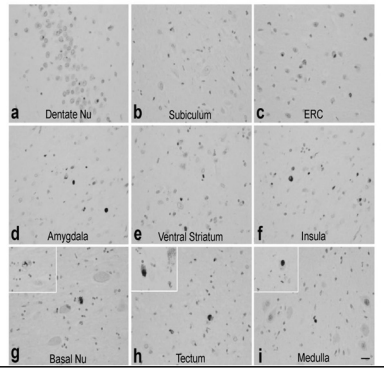
TDP-43



TDP-43

- It has been shown to be common in older brain *(Geser et al., 2010).*
- It is reported to be present in at least 25-66% brains with pathologically confirmed Alzheimer's disease *(Amador-Ortiz et al., 2007, Uryu et al., 2008).*
- It may progress through the brain in a stereotypical manner in patients with Alzheimer's disease pathology *(Josephs et al., 2014, 2016)*
- It is subsequently reported to be associated with Hippocampal sclerosis, LBD, CTE, and cognitively normal Asians *(Nascimento et al., 2016)*

TDP-43 in AD



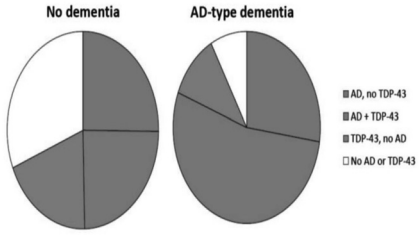
Josephs et al., 2016

TDP-43 in AD

Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6
• Amygdala	• Entorhinal • Subiculum	• Dentate • OTC	• Insula • Ventral striatum • Basal forebrain • Inferior temporal	• Substantia nigra • Inferior olive • Midbrain tectum	• Basal ganglia • Middle frontal

Josephs et al., 2016

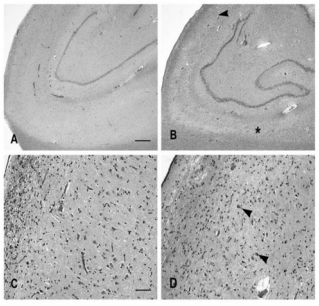
TDP-43 in AD

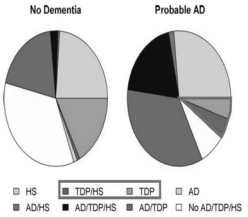


- TDP-34 was associated with greater memory loss and hippocampal atrophy

James et al., 2016

Hippocampal Sclerosis (HS)



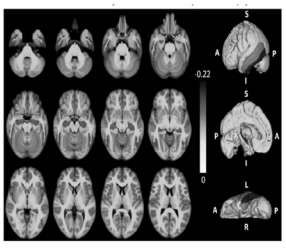


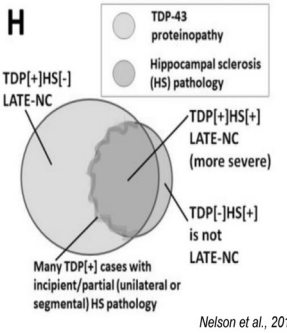
- Blue shades: AD with or without coexisting HS and/or TDP-43 pathology
- Pink shades: HS and/or TDP-43 without AD

Nag et al., 2015

LATE (Limbic-predominant age-related TDP-43 encephalopathy)

- Clinical characteristics





Nelson et al., 2019