“Converging Pathologies In Neurodegenerative Diseases”

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"Fatal Attractions" of Proteins

A Comprehensive Hypothetical Mechanism Underlying Alzheimer’s Disease and Other Neurodegenerative Disorders

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**Abstract:** Abnormal protein–protein interactions that result in the formation of intracellular and extracellular aggregates of proteinacious fibrils are common neuropathological features of many, albeit diverse, neurodegenerative disorders, such as sporadic and familial Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, and prion encephalopathies. Indeed, increasing evidence suggests that abnormal protein–protein interactions and/or the lesions that result from the aggregation of pathological protein fibrils could play a mechanistic role in the dysfunction and death of neurons or glial cells in neurodegenerative diseases. Here we propose that “fatal attractions” between brain proteins are the key pathological events underlying Alzheimer’s disease and a large number of other seemingly diverse neurodegenerative disorders. This hypothesis predicts that the abnormal interaction between normal brain proteins alters their conformation and promotes the assembly of these pathological conformers into filaments that progressively accumulate as intracellular or extracellular fibrous deposits in the central nervous system. Further, the transformation of the normal proteins into pathological conformers is predicted to result in losses of critical functions, and the disease proteins or their progressive accumulation into filamentous aggregates are predicted to acquire neurotoxic properties, all of which culminate in the dysfunction and death of affected brain cells. Thus, the “fatal attractions” hypothesis describes a plausible unifying mechanism that accounts for the onset/progression of Alzheimer’s disease and a large number of other seemingly unrelated neurodegenerative disorders characterized neuropathologically by filamentous brain lesions formed by different proteins.

**Keywords:** Tauopathies; Synucleinopathies; Filamentous inclusions; Protein aggregates


**Penn Medicine Joins Parkinson’s Progression Markers Initiative (PPMI) as Official Study Site and Bioanalytics Core Lead**

*$40-million, Five-Year Observational Clinical Study, Sponsored by Michael J. Fox Foundation, Seeks Biomarkers of Parkinson’s Disease*
The Complexity Of Co-Morbid Protein Deposits In AD, Related Tauopathies And Other Disorders Creates Challenges For Mechanistic Understanding And Drug Discovery.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>LESIONS</th>
<th>COMPONENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alzheimer’s Disease (AD)</strong></td>
<td>SPs (100%) NFTs (100%) LBs (-50%) TDP-43 (-50%)</td>
<td>Aβ Tau Alpha-synuclein TDP-43</td>
</tr>
<tr>
<td>The most common multi-proteinopathy</td>
<td></td>
<td></td>
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<tr>
<td><strong>Frontotemporal Degeneration (FTD)</strong></td>
<td>Inclusions</td>
<td>Tau (FTLD-Tau), TDP-43 (FTLD-TDP), FTLD-FUS</td>
</tr>
<tr>
<td><strong>Amyotrophic Lateral Sclerosis (ALS)</strong></td>
<td>Inclusions</td>
<td>TDP-43, FUS, Tau, SOD1</td>
</tr>
<tr>
<td><strong>Parkinson’s Disease (PD) +/- Dementia (PDD) &amp; Dementia With Lewy Bodies (DLB)</strong></td>
<td>LBs, SPs, NFTs</td>
<td>Alpha-synuclein, Aβ, Tau</td>
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<tr>
<td><strong>Multiple System Atrophy (MSA)</strong></td>
<td>GCIs</td>
<td>Alpha-Synuclein</td>
</tr>
<tr>
<td><strong>Prion Diseases</strong></td>
<td>SPs</td>
<td>Prions, Tau, Aβ, Alpha-synuclein</td>
</tr>
<tr>
<td><strong>Trinucleotide repeat diseases</strong></td>
<td>Inclusions</td>
<td>Expanded polyglumatine repeats</td>
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Daniel Perry, Reisa Sperling, Russell Katz, Donald Berry, David Dilts, Debra Hanna, Stephen Salloway, John Q. Trojanowski, Chas Bountra, Michael Krams, Johan Luthman, Steven Potkin, Val Gribkoff, Robert Temple, Yaning Wang, Maria C. Carrillo, Diane Stephenson, Heather Snyder, Enchi Liu, Tony Ware, John McKew, Alan Fox, F. Owen Fields, Lisa J. Bain, Cynthia Bens

Introduction

Combination drug therapy has proven to be an effective strategy for treating many of the world’s most intractable diseases, from tuberculosis to HIV/AIDS in the 1990s. Thus, it is not surprising that in the face of so many disappointing clinical trials for Alzheimer’s disease (AD) drugs, interest in combination therapy for AD has captured the interest of many investigators in academia, industry, and regulatory agencies, as well as foundations and advocacy organizations.

Next steps for combination therapy

- Establish a leadership group as well as think tanks and workgroups with technical experts as needed to:
  - Develop consensus on the mechanistic rationale for combination therapy,
  - Develop an inventory of targets and develop consensus on prioritizing targets or classes of targets.
  - Inventory compounds and develop a process for promoting compounds for further development.
  - Build an inventory of databases and data repositories to tackle issues that prevent companies from sharing data.
  - Inventory modeling and simulation tools and begin planning how to use these tools to develop combination trials in early AD patients.
  - Develop a clinical trial infrastructure for combination trials (e.g., ADCS, ADNI, DIAN Pharma Consortium) or creating a new partnership.
  - Explore innovative funding mechanisms to begin planning a combination trial.


In this review, we give a brief description of the pathogenesis of AD and provide detailed discussions about the recent development of chemical structures of anti-AD agents (2013 up to present) that have multiple targets, such as amyloid-β peptide, Tau protein, cholinesterases, monoamine oxidase, β-site amyloid-precursor protein-cleaving enzyme 1, free radicals, metal ions (Fe2+, Cu2+, Zn2+) and so on. In this paper, we also added some novel targets or possible pathogenesis which have been reported in recent years for AD therapy.
Fig. 1. Agents in clinical trials for the treatment of Alzheimer’s disease in 2017 (from clinicaltrials.gov accessed 1/5/2017). Abbreviations: ATP, adenosine triphosphate; BNC, bisnorcymserine; GM-CSF, granulocyte-macrophage colony-stimulating factor; OAA, oxaloacetate; IVIG, intravenous immunoglobulin; SLAT, simvastatin + L-arginine + tetrahydrobiopterin.
Can the Neurodegenerative Disease Research Brain Bank at Penn help us answer this question using DNA, RNA, MicroRNA, Fresh/Fixed Neurodegenerative Disease And “Control” Brain Samples To Identify Proteopathic Transmissable Strains, Mechanisms Of Cellular Dysfunction And Death In Neurodegenerative Diseases

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>#</th>
</tr>
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<tbody>
<tr>
<td>Agyrophilic grain disease</td>
<td>9</td>
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<tr>
<td>Alzheimer's disease</td>
<td>576</td>
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<tr>
<td>ALS</td>
<td>150</td>
</tr>
<tr>
<td>ALS-FTD</td>
<td>17</td>
</tr>
<tr>
<td>Anoxia/hemorrhage</td>
<td>15</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy</td>
<td>5</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>50</td>
</tr>
<tr>
<td>Dementia lacking distinctive histopathology</td>
<td>2</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>52</td>
</tr>
<tr>
<td>Down's syndrome</td>
<td>12</td>
</tr>
<tr>
<td>Dentatorubral pallidoluysian atrophy</td>
<td>1</td>
</tr>
<tr>
<td>FTDP-17</td>
<td>7</td>
</tr>
<tr>
<td>FTLD-FUS</td>
<td>5</td>
</tr>
<tr>
<td>FTLD-TDP</td>
<td>110</td>
</tr>
<tr>
<td>FTLD-U</td>
<td>1</td>
</tr>
<tr>
<td>HDLS with axonal spheroids</td>
<td>3</td>
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<tr>
<td>Multiple system atrophy</td>
<td>55</td>
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<tr>
<td>Neurodegeneration with brain iron accumulation</td>
<td>2</td>
</tr>
<tr>
<td>Normal (including PART, low AD, pathologic aging)</td>
<td>257</td>
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<tr>
<td>Parkinson's disease</td>
<td>120</td>
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<tr>
<td>Parkinson's disease dementia</td>
<td>134</td>
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<tr>
<td>Pick's disease</td>
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<tr>
<td>Polyglucosan body disease</td>
<td>2</td>
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<tr>
<td>Prion disease</td>
<td>5</td>
</tr>
<tr>
<td>Progressive subcortical gliosis</td>
<td>1</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>106</td>
</tr>
<tr>
<td>Tangle predominant senile dementia</td>
<td>6</td>
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<tr>
<td>Tauopathy NOS</td>
<td>18</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1752</strong></td>
</tr>
</tbody>
</table>
Comparative Survey of the Topographical Distribution of Signature Molecular Lesions in Major Neurodegenerative Diseases

Steven E. Arnold, Jon B. Toledo, Dina H. Appleby, Sharon X. Xie, Li-San Wang, Young Baek, David A. Wolk, Edward B. Lee, Bruce L. Miller, Virginia M.-Y. Lee, and John O. Trojanowski


To address the issue of the anatomic distributions of major neurodegenerative disease lesions we compared the topography of these lesions in 10 neurodegenerative diseases from a large and uniformly assessed brain collection. Ratings of pathological severity in 16 brain regions from 671 cases with diverse neurodegenerative diseases are summarized in the following slides highlighting the lesion distributions that either overlap or distinguish the diseases in each molecular disease category.
Tau Inclusions In Tauopathies

TDP-43 Inclusions In FLTD-TDP & ALS
Pathological tau, Aβ, alpha-synuclein (a-syn) TDP-43 in 766 longitudinally followed Penn Brain Cases with diverse neurodegenerative disease (ND) from 2000-2013, i.e. 247 AD; 95 tauopathies (PiD, CBD, PSP; 164 synucleinopathies (MSA, LBD; 188 FTLD-TDP) and ALS as well as a group of 72 minimal pathology or control subjects. Age and sex matched logistic regression models were compared for co-pathology between groups. Tau>Aβ>>a-syn>TDP-43 which was rarest. In ALS and neocortical LBD, co-pathologies associated with APOE ε4. LBD cases with AD co-pathology had substantially lower MMSE scores than primary LBD. Our data implies that increased age and APOE ε4 status are risk factors for co-pathologies independent of ND and that ND severity influences co-pathology. These findings have implications for clinical trials that focus on monotherapies targeting tau, β-amyloid, α-synuclein and TDP-43.
Figure 1: Pathological tau, amyloid-β, α-synuclein, and TDP-43 staging. Tau, amyloid-β, α-synuclein, and TDP-43 pathologies were individually staged according to established criteria across 13 neuropathologically-defined groups. (A) Tau pathology principally took the form of Alzheimer’s disease-type neurofibrillary tangles, except in FTLD-Tau (i.e., PiD, CBD, and PSP), allowing us to assign Braak stages and compare tau prevalence and severity (Montine et al., 2012). Co-pathological tau was nearly universal, and was commonly observed in the hippocampal formation (Braak I-II). (B) McKee criteria staging of α-synuclein positive Lewy pathology was applied to all cases except the MSA group (McKeith et al., 2017). α-Synuclein (A-syn) co-pathological affected a minority of cases across neurodegenerative disease and was frequently limited to a brainstem or amygdala distribution except in the hAD group. (C) Amyloid phases were used to stage amyloid-β (Aβ) plaques (Montine et al., 2012). Amyloid-β plaque co-pathology was variably abundant across neurodegenerative disease except the nLBD group, which had an increased burden. (D) Distinct distributions of TDP-43 pathology defined the primary TDP-43 proteinopathies, but a common staging was possible for the remaining groups (Josephs et al., 2014). TDP-43 was rare to non-existent in several groups and frequently had a limbic distribution.
Pie Charts Of Co-Pathologies In Diverse Neurodegenerative Diseases

Co-Pathologies

Primary ND

- Pure
- No pathology

Co-pathologies

- Aβ
- A-syn
- TDP-43

Multi-pathologies

- Aβ/TDP-43
- A-syn/TDP-43
- Aβ/a-syn/TDP-43

Legend:

- Solid line: with tau

Examples:

C:

ALS

- a-syn
- Aβ
- Pure TDP-43 60%

FTLD-TDP

- Aβ
- Pure TDP-43 53%

hTDP

- Aβ
- Pure TDP-43 60%

D:

βLBD

- Aβ
- Pure a-syn 50%

τLBD

- TDP
- Aβ
- Pure a-syn 32%

nLBD

- Aβ
- Pure a-syn 19%

MSA

- Aβ
- Pure a-syn 62%
Pie Charts Of Co-Pathologies In Diverse Neurodegenerative Diseases
Common neurodegenerative co-pathologies

Figure 3  Alzheimer’s disease neuropathological change co-pathology. The level of ADNPC was measured in all groups (Montine et al., 2012). Intermediate and high levels of ADNPC were rare except in the PSP and nLBD group. Definite and possible PART was common across the majority of groups (Crary et al., 2014). AD = Alzheimer’s disease; MPG = minimal pathology group.
Non-Alzheimer’s contributions to dementia and cognitive resilience in The 90+ Study

John L. Robinson¹ · Maria M. Corrada² · Gabor G. Kovacs¹,³ · Myrna Dominique¹ · Carrie Caswell⁴ · Sharon X. Xie⁴ · Virginia M.-Y. Lee¹ · Claudia H. Kawas⁵ · John Q. Trojanowski¹

The diagnosis of AD in the oldest-old is complicated by increasing age-related tangles, plaques and non-AD pathologies such as cerebrovascular disease (CVD), hippocampal sclerosis (HS), aging-related tau astrogliopathy (ARTAG), as well as TDP-43 and LB. We assessed the levels of these pathologies in brain so 185 90+ Study. 53% had dementia, primarily AD or mixed AD; 23% had cognitive impairment without dementia (CIND); 23% were not impaired. By NIA-AA criteria and dementia status, the cohort was subdivided into four groups: those with minimal ADNPE included the not dementia (ND) and Not AD dementia groups; and those with significant ADNPE included the Resilient without dementia and AD dementia groups. Compared to the ND group, the Not AD dementia group had more HS, cortical ARTAG, TDP-43, and LBs. Compared to the AD dementia group, the Resilient group had less CVD, no HS and less cortical ARTAG, TDP-43 and LB pathology. Our findings imply that non-AD pathologies including CVD contribute to cognitive resilience in the oldest-old.
ARTAG In The 90+

Figure 3. Conceptual summary of the development of astroglial tau pathologies.

Tufted astrocyte  \( \rightarrow \) Astrocytic plaque  \( \rightarrow \) Globular astroglial inclusion

Scattered \( \tau \text{+} \) dots in astrocytic processes \( \rightarrow \) Accumulation of \( \tau \text{+} \) immunoreactivity in processes and perinuclear region

Granular/fuzzy astrocyte 1  \( \rightarrow \) Granular/fuzzy astrocyte 2  \( \rightarrow \) Ramified astrocyte

MINI-SYMPOSIUM: Astroglia in Neurodegenerative Diseases

Protein astrogliopathies in human neurodegenerative diseases and aging

Gábor O. Kovács, Virginia M. Lee, John Q. Trojanowski^3

1 Institute of Neurology, Medical University of Vienna, Vienna, Austria
2 Center for Neurodegenerative Disease Research, Institute on Aging and Department of Pathology and Laboratory Medicine of the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.

Fig.1 ARTAG pathology. Limbic (a-d), brainstem (e-g) and neocortical (h) ARTAG in The 90+ study. a Severe GFA in gray matter of the amygdala. b Severe TSA in the temporal lobe. c ARTAG frequently co-exists with AD tau pathology. Substantial white matter TSA underlying a severe burden of NFTs in the entorhinal cortex. d Subependymal TSA in the lateral ventricle. e TSA in the medial lemniscus and inferior olive nucleus. f TSA and GFA in the spinal lemniscus in the mesencephalon. g Perivascular TSA around the cerebral aqueduct. h Gray matter GFA in the temporal cortex. Scale bar is 100 \( \mu \text{m} \) in all images. ARTAG aging-related tau astrogliopathy. GFA granular fuzzy astrocytes, TSA thorn-shaped astrocytes.
Fig. 2 Pathological associations with Braak stages. Non-AD pathology and plaque pathology are graphed by increasing Braak stage. Non-AD pathology includes TDP-43 stage and Lewy pathology (lines, on the right axis) as well as HS, cortical ARTAG and CVD (histogram, frequency indicated by the right axis), while plaque pathology is represented as NIA-AA criteria A0-3 and C0-3 values (lines, on the left axis). At low Braak stages (I–III): definite CVD is prevalent in about 15% of individuals; HS and cortical ARTAGs are rare, as are TDP-43 and Lewy pathologies; plaques are restricted to cortical areas (A1) and are only rarely neuritic (C1). At high Braak stages (IV–VI): definite CVD increases to over 30% \((p=0.009)\); HS increases to over 20% \((p=0.006)\); cortical ARTAG increases to over 30% \((p<0.001)\); TDP-43 is commonly found in the amygdala \((p<0.001)\) but Lewy pathology remains rare; plaques are more widespread (Thal phase, \(p<0.001\)) and neuritic (CERAD, \(p\leq 0.001\)). See Supplemental Table 3 for the full statistics including OR and 95% CI for each measure’s association with Braak stage and Thal phase. ARTAG aging-related tau astroglialopathy, CVD cerebrovascular disease, HS hippocampal sclerosis.
Table 5 Non-AD associations with dementia in both the Not AD dementia and AD dementia groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>TDP-43 stage</td>
<td>1.87</td>
<td>(1.31, 2.66)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lewy pathology</td>
<td>1.83</td>
<td>(1.08, 3.09)</td>
<td>0.024</td>
</tr>
<tr>
<td>Limbic ARTAG</td>
<td>0.99</td>
<td>(0.76, 1.30)</td>
<td>0.96</td>
</tr>
<tr>
<td>Brainstem ARTAG</td>
<td>0.94</td>
<td>(0.66, 1.34)</td>
<td>0.73</td>
</tr>
<tr>
<td>Cortical ARTAG</td>
<td>2.23</td>
<td>(1.23, 4.04)</td>
<td>0.008</td>
</tr>
<tr>
<td>Definite CVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not AD dementia vs. ND</td>
<td>1.04</td>
<td>(0.39, 2.79)</td>
<td>0.93</td>
</tr>
<tr>
<td>AD Dementia vs. Resilient</td>
<td>7.18</td>
<td>(1.97, 26.18)</td>
<td>0.003</td>
</tr>
<tr>
<td>HS</td>
<td>14.99</td>
<td>(3.41, 65.93)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*ARTAG* aging-related tau astrogliopathy, *CVD* cerebrovascular disease, *HS* hippocampal sclerosis
Neuropathological Substrates of Dementia in PD

- 140 autopsy-confirmed PD/PDD UPENN patients.
- Clinical diagnosis of Parkinson’s disease (with or without dementia).

Neuropathologic Substrates of Parkinson Disease Dementia

David J. Irwin, MD, Matthew T. White, MS, MPH, Jon B. Toledo, MD, Sharon X. Xie, PhD,
John L. Robinson, BS, Vivianna Van Deerlin, MD, PhD, Virginia M.-Y. Lee, PhD, MBA,
James B. Leverenz, MD, Thomas J. Montine, MD, PhD, John E. Duda, MD,
Howard I. Hurtig, MD, and John Q. Trojanowski, MD, PhD

ANN NEUROL 2012;72:587-598
Neuropathological Substrates of Dementia in PD

Clinical, pathologic and genetic variables examined

- TAU NFTs, Aβ SPs, SYN CLB/LN:
  - Global cortical severity scores (average of 5 regions)
  - Stage of pathology (Braak, CERAD, McKeith LBD stage)
  - Basal ganglia neuropathological severity scores
- Hippocampal CA region 2/3 dystrophic LN score
- Presence of cerebrovascular disease (CVD)
- Severity of cerebral amyloid angiopathy (CAA)
- Presence of hippocampal sclerosis (HpScl)
- Presence of argyrophilic grain disease (AGD)
- APOE 4 allele status
- MAPT H1/H1 haplotype status

Limbic TDP-43 pathologic burden

Demographics: Age of onset and death, gender, disease duration, motor-dementia and death-dementia interval

## Neuropathological Substrates of Dementia in PD

### PDD+AD (28.6%)

- Older age of onset
- Higher burden of Lewy pathology
- Shorter time to dementia

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<table>
<thead>
<tr>
<th></th>
<th>PDD With AD N=34</th>
<th>PDD Without AD N=55</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Motor Onset (y)</td>
<td>69.00 (63.75, 73.50)</td>
<td>60.00 (50.00, 68.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age of Dementia Onset (y)</td>
<td>76.00 (73.00, 80.00)</td>
<td>73.00 (64.00, 77.00)</td>
<td>0.009</td>
</tr>
<tr>
<td>Age of Death (y)</td>
<td>79.00 (76.75, 84.25)</td>
<td>77.00 (70.00, 81.00)</td>
<td>0.012</td>
</tr>
<tr>
<td>Disease Duration (y)</td>
<td>10.00 (8.00, 13.25)</td>
<td>15.00 (10.00, 20.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Motor-Dementia Interval (y)</td>
<td>7.00 (4.00, 11.25)</td>
<td>9.00 (5.00, 14.00)</td>
<td>0.013</td>
</tr>
<tr>
<td>Dementia-Death Interval (y)</td>
<td>3.00 (2.00, 6.00)</td>
<td>4.00 (2.00, 6.00)</td>
<td>0.592</td>
</tr>
<tr>
<td>APOE4 N (% carriers)</td>
<td>17/33 (51.5%)</td>
<td>21/55 (41.2%)</td>
<td>0.365</td>
</tr>
</tbody>
</table>
AD Co-pathology in LBD

- Multi-center cohort of autopsy-confirmed clinical LBD
  - PDD=115
  - DLB=98
- Examination of neuropathological correlates of motor-dementia interval and overall survival.

Hypothesis: Coincident AD neuropathology is influential on the onset of dementia and overall survival across PDD/DLB.

Neuropathological and genetic correlates of survival and dementia onset in synucleinopathies: a retrospective analysis


www.thelancet.com/neurology  Vol 16  January 2017
AD Co-pathology in LBD

Irwin et al, *Lancet Neurol* 2017
Cortical SYN, tau and Aβ are correlated \((r=0.4-0.6, \ p<0.0001)\).
Cortical SYN pathology is associated with dementia in LBD.

AD neuropathology is common in LBD (~50%) and confers higher SYN pathology, earlier onset of dementia and death in a dose dependent manner.

*Future clinical criteria and trials should focus on stratifying LBD patients by the presence or absence of AD-related biomarkers.*
Higher antemortem CSF t-tau and lower Aβ_{1-42} levels are predictive of **both increasing cerebral AD and SYN pathology** in LBD.

CSF t-tau and Aβ_{1-42} may identify LBD patients vulnerable to cortical SYN pathology and worse prognosis.
Clinical Correlates of AD co-pathology in LBD

- Tau co-pathology associates with higher SYN pathology in temporal-parietal regions.
- This distribution is altered from pure AD without SYN co-pathology.
- AD co-pathology may have specific clinical features based on temporally mediated cognitive functions.
Genetic Associations with Phenotypic Heterogeneity in LBD

- APOE 4 allele associated with more temporally-mediated cognitive functions\(^1\)
  - APOE 4 allele in SYN+AD>SYN-AD>controls\(^2\)
- GBA mutations/E326K variant associated with postural/instability (PIGD) and more rapid decline\(^3\).
- GBA mutations/E326K variant associated with frontal-executive/visuospatial cognitive impairments\(^4\).
  - GBA mutations/variant in SYN-AD>SYN+AD>controls\(^5\)
- SNCA risk variant is associated with Tremor-Dominant (TD) PD and more benign prognosis\(^6\)
- LRRK2 associated with PIGD\(^7\) and normal cognition\(^8\).

1 Mata et al JAMA Neurol 2014, 2 Tsuang et al JAMA Neurol 2013, 3 Davis et al, JAMA Neurol 2016, 4 Mata et al Mov Disord 2016
Cross-seeding as a possible mechanism driving co-pathologies
Tau & A-syn In Contursi Family Members With PD, Dementia & A53T Mutations

Concurrence of α-synuclein and tau brain pathology in the Contursi kindred
Thanks To All In CNDR And Our Collaborators

Supported by grants from NIH/NIA/NINDS, the Ware Alzheimer’s Program, and the families of our patients.