The Lewy Body Dementias

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What is Lewy Body Dementia?

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Overview

- What is a Lewy body?
- What are the Lewy body dementias?
- How common is Lewy body dementia?
- What are the needs moving forward?

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What is a Lewy Body?

Frederick Lewy

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Parkinson's Disease

- **Tremor (resting)**
- **Rigidity**
- **Bradykinesia**
- **Postural instability**

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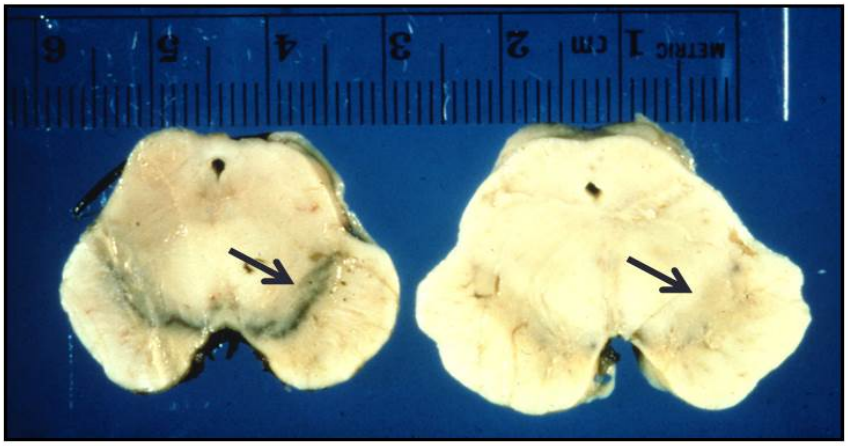
Pathology in Parkinson's Disease

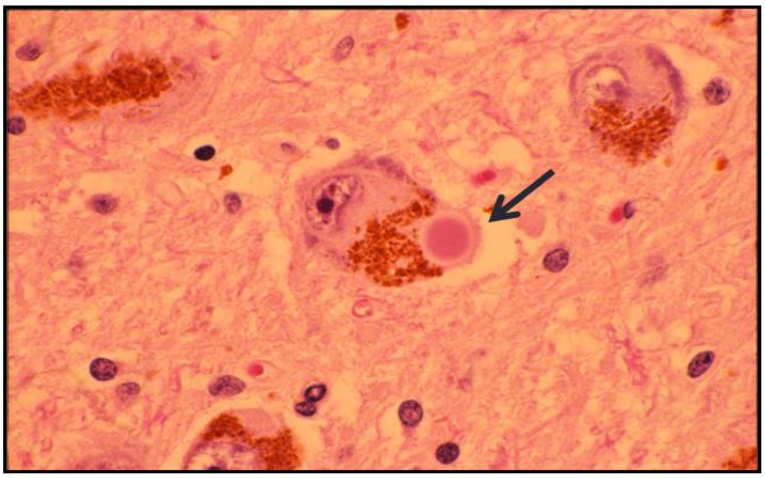
- Clinical history of parkinsonism
- Neuronal loss and ***Lewy body inclusions*** in the substantia nigra, locus coeruleus, basal forebrain and cerebral cortex

Pathology in Parkinson's Disease



Substantia Nigra

Lewy Body Pathology



H&E Stain

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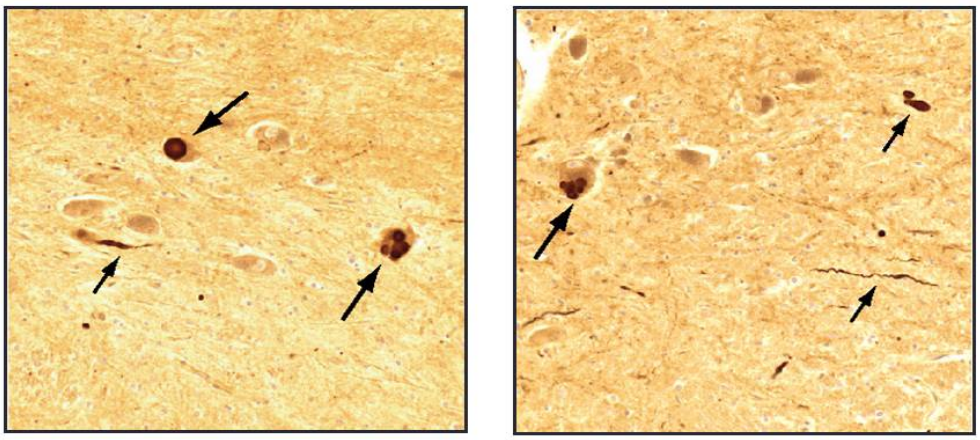
Lewy Body Pathology

- Mutations in ***alpha-synuclein*** gene linked to Parkinson's disease
- Duplications of alpha-synuclein gene linked to Parkinson's disease and dementia with Lewy bodies
- All Lewy bodies have alpha-synuclein protein
- Increased ability to detect Lewy body changes in brain studies

Lewy Body Pathology



α-synuclein IHC

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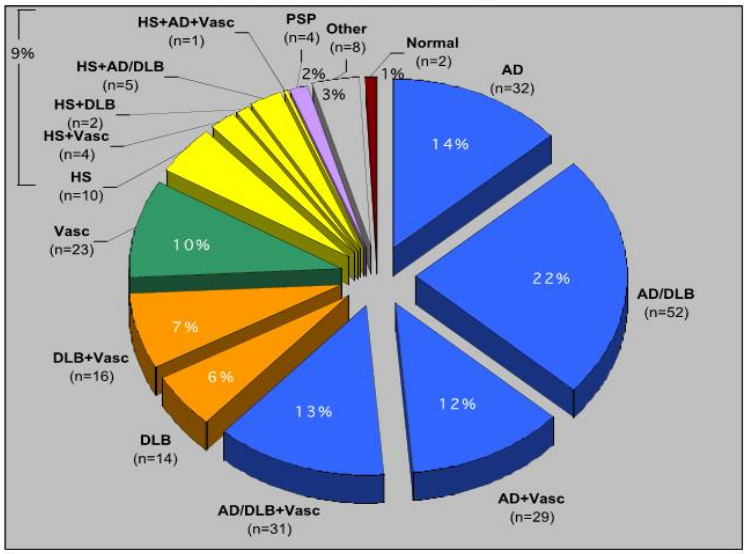
Neuropathology of a Community Based Dementia Sample



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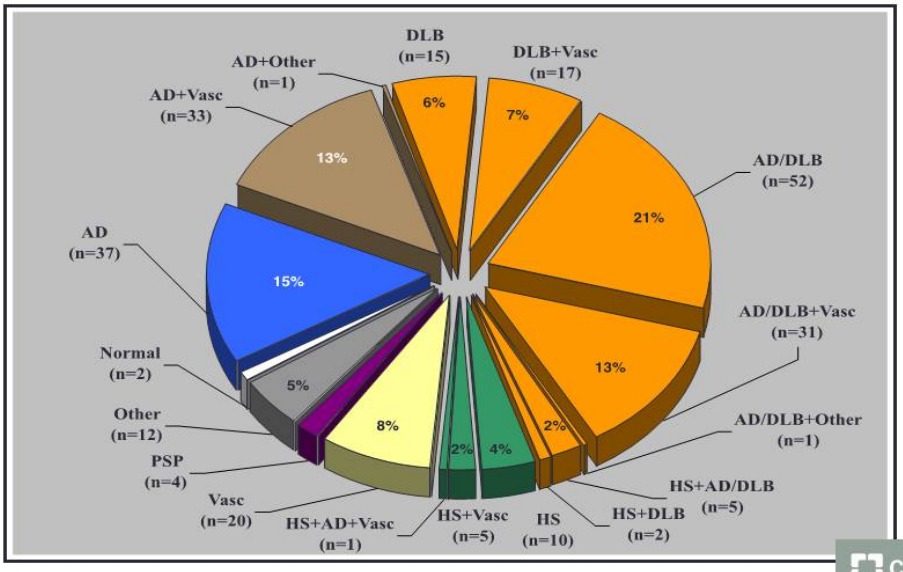
Neuropathology of a Community Based Dementia Sample



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The Lewy Body Dementias

Dementia with Lewy Bodies
Parkinson's Disease Dementia

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Consensus Criteria for Dementia with Lewy Bodies (DLB)

1. …*progressive cognitive decline* of sufficient magnitude to interfere with normal social or occupational function… ("dementia")
2. Core features (2 = "probable", 1 = "possible")
   a. fluctuating cognition, attention, alertness
   b. recurrent visual hallucinations
   c. spontaneous features of parkinsonism
3. Suggestive features (plus one core = "probable" DLB)
   a. REM sleep behavior disorder
   b. severe neuroleptic sensitivity
   c. low dopamine transporter uptake (PET/SPECT)
4. One year rule for DLB vs. Parkinson's Disease Dementia

McKeith I, et al. Neurology 2005

Formed Visual Hallucinations

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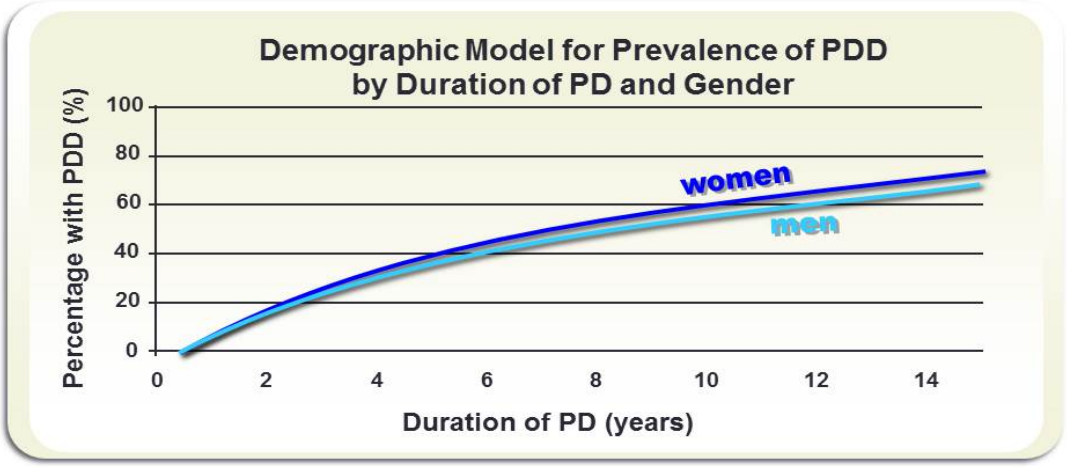
Dementia in Parkinson's Disease



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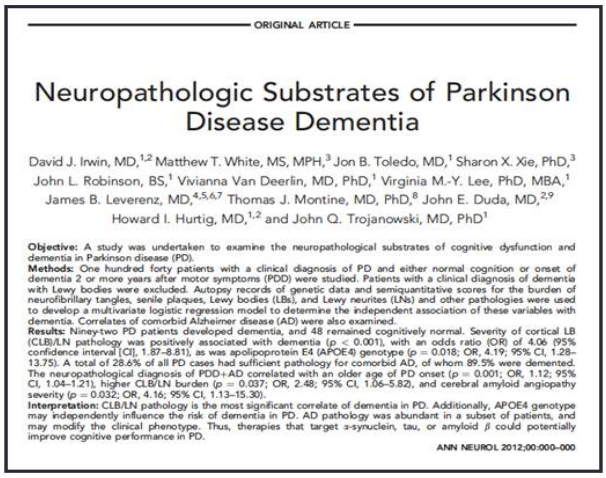
Pathology of Parkinson's Disease Dementia



ORIGINAL ARTICLE

Neuropathologic Substrates of Parkinson Disease Dementia

David J. Irwin, MD,[1,2] Matthew T. White, MS, MPH,[3] Jon B. Toledo, MD,[1] Sharon X. Xie, PhD,[3] John L. Robinson, BS,[1] Vivianna Van Deerlin, MD, PhD,[1] Virginia M.-Y. Lee, PhD, MBA,[1] James B. Leverenz, MD,[4,5,6,7] Thomas J. Montine, MD, PhD,[8] John E. Duda, MD,[2,9] Howard I. Hurtig, MD,[1,2] and John Q. Trojanowski, MD, PhD[1]

Objective: A study was undertaken to examine the neuropathological substrates of cognitive dysfunction and dementia in Parkinson disease (PD).
Methods: One hundred forty patients with a clinical diagnosis of PD and either normal cognition or onset of dementia 2 or more years after motor symptoms (PDD) were studied. Patients with a clinical diagnosis of dementia with Lewy bodies were excluded. Autopsy records of genetic data and semiquantitative scores for the burden of neurofibrillary tangles, senile plaques, Lewy bodies (LBs), and Lewy neurites (LNs) and other pathologies were used to develop a multivariate logistic regression model to determine the independent association of these variables with dementia. Correlates of comorbid Alzheimer disease (AD) were also examined.
Results: Ninety-two PD patients developed dementia, and 48 remained cognitively normal. Severity of cortical LB (CLB/LN pathology was positively associated with dementia ($p < 0.001$), with an odds ratio (OR) of 4.06 (95% confidence interval [CI], 1.87–8.81), as was apolipoprotein E4 (APOE4) genotype ($p = 0.018$; OR, 4.19; 95% CI, 1.28–13.75). A total of 28.6% of all PD cases had sufficient pathology for comorbid AD, of whom 89.5% were demented. The neuropathological diagnosis of PDD+AD correlated with an older age of PD onset ($p = 0.001$; OR, 1.12; 95% CI, 1.04–1.21), higher CLB/LN burden ($p = 0.037$; OR, 2.48; 95% CI, 1.06–5.82), and cerebral amyloid angiopathy severity ($p = 0.032$; OR, 4.16; 95% CI, 1.13–15.30).
Interpretation: CLB/LN pathology is the most significant correlate of dementia in PD. Additionally, APOE4 genotype may independently influence the risk of dementia in PD. AD pathology was abundant in a subset of patients, and may modify the clinical phenotype. Thus, therapies that target α-synuclein, tau, or amyloid β could potentially improve cognitive performance in PD.

ANN NEUROL 2012;00:000–000

- **140 autopsied cases**
- **Links to dementia**
  - **Lewy pathology**
  - ***APOE ε4***
  - **AD (~ 30%)**

Irwin DJ, et al. Ann Neurol 2012

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Dementia with Lewy Bodies

- Criteria good predictor of Lewy body pathology (with or without concomitant AD pathology) - *high positive predictive value*
- Criteria poor predictor of the absence of Lewy body pathology - *low negative predictive value*
- ***Pathology in DLB identical to PDD except for higher coexiting AD pathology***

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Lewy Body Pathology in Alzheimer's Disease

- High frequency in AD
  - Using ASN immunohistochemistry and amygdala sampling
  - 63% PS-1/APP mutation AD
  - 50% of Down syndrome
  - 61% of "sporadic" AD
  - 64% PS-2 mutation AD

Leverenz et al, Arch Neurol, 1986; Ditter et al, Neurology, 1987; Hamilton, Brain Path, 2000, Lippa, Lippa et al, AJP, 1998; Lippa et al Ann Neurol, 1999; Leverenz et al, Arch Neurol, 2006

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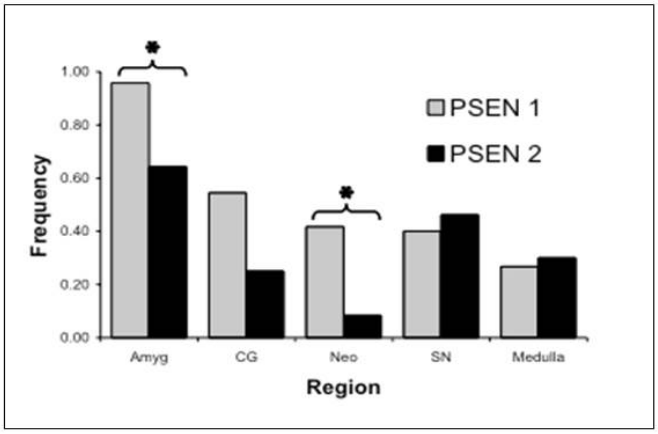
Lewy Body Pathology in Alzheimer's Disease



Leverenz et al, Arch Neurol, 2006

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DLB, PDD and Alzheimer's Disease

- Is DLB just a variant of PD/PDD?
  - Similar Lewy body pathology
  - Some shared genetics (e.g., *GBA*)
- Is DLB just a variant of AD?
  - Frequent AD pathology in DLB
  - Some shared genetics (e.g., *APOE*)
- We don't know
  - Likely shared risks contribute to the clinical and pathological picture

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National Plan to Address Alzheimer's Disease: 2015 Update

Goals as Building Blocks for Transformation

Achieving the vision of eliminating the burden of ADRD starts with concrete goals. Below are the five that form the foundation of this National Plan:

1. Prevent and Effectively Treat Alzheimer's Disease by 2025.
2. Enhance Care Quality and Efficiency.
3. Expand Supports for People with Alzheimer's Disease and their Families.
4. Enhance Public Awareness and Engagement.
5. Track Progress and Drive Improvement.

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Lewy Body Dementias – Positive

- Increasing recognition of dementia in PD
  - Focus of two NINDS sponsored Udall Centers
  - Increasing funding from other sources (MJFF)
- First international DLB meeting in 10 years
- NIA sponsored DLB module
- Increasing interest from industry
- Lewy Body Dementia Association
  - Expanding programs, "Lewy Who"

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Lewy Body Dementias – Negative

- 1.4 Million Americans
  - DLB, PDD, and LBV-AD
- Clinical care
  - Multiple visits before diagnosis, misdiagnosis
  - Inappropriate care (e.g., antipsychotics)
  - Patient and family distress
  - Access to long term care
- Research
  - Consistent and coordinated research and funding (DLB)

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Thank You

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