The Lewy Body Dementias

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What is Lewy Body Dementia?

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LEWY WHO?
Lewy Who Continues to Impact Awareness
Overview

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

What is a Lewy Body?

Frederick Lewy
Parkinson’s Disease

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

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
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

α-synuclein IHC
The Lewy Body Dementias

Dementia with Lewy Bodies
Parkinson’s Disease Dementia

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

Dementia in Parkinson’s Disease

Demographic Model for Prevalence of PDD by Duration of PD and Gender
Pathology of Parkinson’s Disease Dementia

Neuropathologic Substrates of Parkinson Disease Dementia

Objectives: 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, or more than 2 years after onset of symptoms (POD) were studied. Patients with a clinical diagnosis of dementia were identified through case note review. Neuropathologic substrates included Lewy bodies, Lewy neurites, and neuritic plaques, and were identified in the substantia nigra, substantia nigra, locus ceruleus, and globus pallidus. The parkinsonian limbs were used to develop a multi-factorial logistic regression model to determine the independent association of these variables with dementia.

Results: The prevalence of AD pathology in PD was significantly associated with dementia (Odds Ratio = 8.5; 95% Confidence interval = 3.1-8.6), with an odds ratio (OR) of 4.8 (95% CI = 1.2-17.8) less than 2 years after PD onset and a lower pathology for dementia (OR = 1.5, 95% CI = 0.9-2.5) when 50 years after PD onset. The odds ratio was 5.0 (95% CI = 1.2-20.0) for dementia on the CVC (1.2-1.7). Higher CVC burden (OR = 0.027, 95% CI = 0.020, 0.032) was independently associated with dementia in PD. AD pathology was associated with dementia in PD, and may independently influence the risk of dementia in PD. AD pathology was associated with a reduction in PD, and may modify the clinical phenotype. Thus, targeting the target population, i.e., patients with PD, is likely to improve cognitive performance in PD.

140 autopsied cases
- Links to dementia
  - Lewy pathology
  - APOE e4
  - AD (~30%)

Dementia with Lewy Bodies

- Criteria good predictors 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 coexisting AD pathology
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

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

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.
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”

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)
Thank You