Dementia Comes to Parkinson Disease

John H. Growdon, M.D.
AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

FELLOW OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

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1817.

AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. (L'atonia Agitans.)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

The term Shaking Palsy has been vaguely employed by medical writers in general. By some it has been used to designate or-
Statuette d’une femme atteinte de la maladie de Parkinson

Platre patine de Paul Richer
Cardinal Signs of PD

- Resting Tremor, often unilateral onset
- Muscular Rigidity, often “cogwheel”
- Bradykinesia
- Gait abnormality, often with reflex postural impairment

- Non-motor symptoms, e.g. depression, RBD, loss of smell, constipation & cognitive impairments, often leading to dementia
Cognitive Tests in 66 Non-Demented PD Patients Revealed Impairments in Specific Domains

• Boston Naming & Verbal Fluency
• Stroop Color Naming
• Picture Arrangement
• Story Recall (after 10 minute delay)
• Benton Visual Recognition
• Raven’s Matrices
The proportion of patients with at least one Specific Cognitive Impairment increased across Hoehn & Yahr stage of PD:

- Stage 1: 40%
- Stage 2: 65%
- Stage 3: 75%
- Stage 4: 86%  

Growdon, Corkin, Rosen 1990

Are these isolated cognitive impairments signs of impending dementia?
Cognitive Impairments & Dementia in PD

Epidemiological survey in Cambridgeshire.  
(Foltynie et al. *Brain* 2004;127:550-560)  
Point prevalence = 36%

Review of 36 prevalence studies.  
Point prevalence = 31%

Population-based cohort study in Rotterdam.  
Risk of dementia in PD 2.8x greater than in non-PD population
Incidence Rates of Dementia

• For MCI, estimates range between 10-15%

• Risk factors include advancing age, head injury, & APOE ε4.

• For idiopathic PD, estimates range between 3-10%. In our MGH series, it was 3.8%

• Risk factors include advancing age, duration of PD, stage of PD severity, plus ?
Advent of diffuse Lewy body disease and dementia with Lewy bodies (DLB)


Of 79 autopsied dementia cases in his hospital, 43.6% were AD and 15.4% were DLB. He first proposed in 1976 the term “diffuse Lewy body disease” and specified two forms: “common” which has AD pathology and “pure” which has none.

Consensus Criteria for the Clinical Dx DLB - 1996

- Progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function.
- For **PROBABLE DLB**, 2 of the 3 following features: fluctuating cognition with variations in attention/alertness, recurrent visual hallucinations that are well formed, and spontaneous motor features of parkinsonism.
- For **POSSIBLE DLB**, only 1 of the 3 core features is required.
- Supportive features: falls, syncope, neuroleptic sensitivity, systematized delusions and non-visual hallucinations.
Diagnostic categories of PD based on cognitive criteria

- **Idiopathic PD**: No cognitive complaints and normal scores on cognitive tests.

- **PD-MCI**: Cognitive complaint by patient or close family member + impairment on at least 1 cognitive test.

- **PDD**: Dementia becoming apparent after many years of motor symptoms but normal cognition

- **DLB**: Dementia with onset around the same time as PD motor symptoms
The PD, PD-MCI, PDD & DLB Cognitive Spectrum

<table>
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<th>Cognition, at onset</th>
<th>MCI</th>
<th>% Demented at death</th>
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<td>PD-normal</td>
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<td>PD-MCI</td>
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<td>PD-D</td>
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<td>85%</td>
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<td>DLB</td>
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Questions that sparked our research program

1. Does PD-MCI always lead to PDD?
2. Are the factors that lead to MCI and dementia differ from those that cause progressive motor impairments?
3. What are the pathological (anatomic/biochemical/molecular) changes that lead to cognitive impairment and to dementia? Can we detect these during life?
4. Are the factors that start the chain of events leading to MCI and dementia the same as those that actually cause these impairments? Is there a single trigger for disease, or a cascade of separate events?

To address these and related questions, Steve Gomperts and I worked with a multi-disciplinary team to study parkinsonian patients with careful neurological, neuropsychological, neuroimaging and ultimately neuropathological examinations. Foremost have been Keith Johnson (PET scans), Dorene Rentz (neuropsychology), Mathew Frosch (neuropathology) and Joe Locascio (statistics).

Implications stemming from successful completion of the research would be to clarify the pathologic bases of dementia in PD and then to identify specific targets for drug development, including the optimal time to apply such treatments.
There is extensive atrophy in the nuclei of the ventral forebrain in PD, that is especially severe in PDD.

A = control nbM  
B = PDD nbM

Whitehouse et al., 1983
CAT activity in frontal cortex is significantly decreased in PD p<.01 but especially in PDD (p<.001) compared to control values.

Dubois et al., 1983
Rivastigmine, an AChEI, was associated with modest improvement in symptoms in 410 PD patients with mild-to-moderate dementia.

A. Change from baseline in the ADAS-cog score.
B. CGCI scores at 24 weeks.

A new look into the basis of dementia in LBDs

- Concomitant AD pathology with neuritic Aβ plaques, which can be detected in life with amyloid Aβ radioligands.
- Dopaminergic striatal & frontal-lobe deficit due to degeneration of brain stem DA nuclei, which can be indexed by tropane radioligands.
- Neurofibrillary tangles, which can be detected with tau imaging.
- Diffuse Lewy bodies and α-synuclein neurites in neocortex. There are no radioligands for α-synuclein but the resultant synaptic loss can be estimated by neurodegeneration on MRI and/or with FDG imaging.
Representative PIB images from a 75 year old normal control, 79 year old AD, 65 year old PD, 69 year old PDD and 71 year old DLB.
PiB binding varies significantly (*p<0.05) across diagnostic groups.

Each point represents a single subject. Cases with specific cortical uptake of PiB are shown in closed circles; cases with low non-specific binding are shown as open circles.

PiB uptake at baseline in 35 non-demented PD subjects
the open circles = normal cognition (n = 20); the closed circles = PD-MCI (n = 15)
the dashed line denotes the point separating PiB + from PiB -

PiB uptake at baseline did not distinguish PD-normal from PD-MCI
Among 35 non-demented PD patients followed for 5 years, higher PiB uptake (green dashed line) predicted faster conversion of diagnosis from PD to PD-MCI/PDD (n=10) and PD-MCI to PDD (n=5). $P < 0.008$
PiB uptake is highest in DLB, followed by PDD > PD-MCI > PD

* p < .001
Amyloid burden significantly accelerates cognitive decline in DLB and PDD.

Subject slopes predicted by fixed(circles) & random(squares, empirical Bayes estimates) effects.
Neurodegeneration, as indexed by cortical thinning, is exacerbated by Aβ burden.
Interim Conclusion

1. Aβ amyloid is common in PD
2. Aβ amyloid doesn’t discriminate PD-nl from PD-MCI
3. Aβ amyloid is not benign, but increases the risk of developing MCI and dementia
4. Aβ deposits are complicit in worsening neurodegeneration.
5. High amounts of Aβ in cerebral cortex are common in DLB (and to a lesser extent in PDD) and increase the rate of cognitive decline
α-synuclein + Aβ

PDD

DLB

α-synuclein

Aβ + α-synuclein

PD

DLB-EPS

α-synuclein
Altropane PET images

HCS

DLB
Altropane DAT scans distinguish Lewy body diseases from Alzheimer disease
The putamen and caudate (shown here) altropane signal was significantly reduced in both parkinsonian groups.
The altropane signal in the caudate was significantly correlated with decreased cognitive performance in the PD dementia group, as judged by CDR-sb (shown here) and by lower MMSE scores.

* p<0.0001
Interim Conclusion

Dopamine deficiency due to substantia nigra degeneration contributes to cognitive impairment in PD, but by itself is not sufficient to cause dementia.
18F T807
(AV1451)

- Rapid uptake and washout of tracer from brain
- Low white matter binding
- Immunochemistry of tau aggregates in autopsy specimens

Chien et al., JAD 2013; Xia et al., Alz and Dem 2013
[F-18]AV-1451 stains tau in tangles but not α-synuclein in Lewy bodies

Marquie et al. Ann Neurol. 2015;78:787-800
$^{18}$F T807 (AV-1451) PET in Parkinson disease
Tau disposition is increased in PD-impaired and in DLB, sometimes independent of Aβ burden.

* P < 0.03
Tau positive neurofibrillary tangles in the inferior temporal lobe are significantly (p< 0.03) correlated with cognitive impairments in PDD & DLB.

Gomperts et al. *JAMA Neurol* 2016
Tau positive neurofibrillary tangles in the inferior temporal lobe also correlate significantly (p<0.006) with a global measure of behavior (the CDR sum of box score) in patients with PDD and DLB.

Gomperts et al.  *JAMA Neurol* 2016
Conclusions

1. High amounts of Aβ in the cortex increase the risk of developing cognitive impairments and dementia in PD, and when these are present, accelerate the rate of decline.
2. Dopamine deficiency contributes to cognitive impairment in PD; DAT scans are useful in discriminating DLB/PDD from Alzheimer disease.
3. Neurofibrillar tangles imaged with the tau radioligand correlate best with clinical measures of cognitive impairment in PDD and DLB.
Neuroimaging-neuropathological correlation
Aims:

• To validate amyloid molecular imaging against neuropathological findings in PDD and DLB, and

• To examine the concordance among the aggregated proteins Aβ, tau and α-synuclein that characterize the brains of PDD and DLB patients.
Methods

- This study is based on findings from 18 Lewy body disease patients who had amyloid imaging with [11C] PiB during life and comprehensive neuropathological examination after death. 10 of the 18 also had Altropane DAT scans.
- At death, all 18 patients had cognitive impairment & confirmed LBD.
- [11C] PiB scans based on 5-10 mCi. Retention (SUVR 40-60 minutes) was measured in an aggregate ROI comprised of frontal, lateral and retrosplenial regions with whole cerebellar reference.
- Neuropathological examinations scored Braak Lewy bodies, Thal distribution of amyloid, CERAD neuritic plaques, total amyloid plaque burden and Braak neurofibrillary tangles. These measurements were made independent from clinical diagnosis and results of imaging.
### Subject Characteristics

All subjects had cognitive impairment by the time of death

Mean age at PET = 73.6 (57.7-83.9)

Mean interval PiB-death = 4.4 years (0.2-7.6)

10 patients had Altropane DAT scans

<table>
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<tr>
<th>Patient No.</th>
<th>Clinical Dx at PET</th>
<th>Sex</th>
<th>Age at PET</th>
<th>Final Clinical Dx</th>
<th>MMSE</th>
<th>Disease onset – PiB (altropane) (yrs)</th>
<th>PiB (altropane) – autopsy (yrs)</th>
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### PET and Neuropathological Findings

#### All 18 confirmed Lewy body disease

Altropane DAT uptake was reduced in 10/10

PiB accurately detected Aβ amyloid deposits

<table>
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<tr>
<th></th>
<th>PiB SUVR</th>
<th>DAT SUVR</th>
<th>Pathologic Diagnosis</th>
<th>Lewy Body Stage</th>
<th>Nigral Cell Loss</th>
<th>Thal phase</th>
<th>NFT stage</th>
<th>Neuritic Plaque score</th>
<th>CAA severity</th>
<th>Sup. Frontal</th>
<th>Sup. Parietal</th>
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</table>

**Total amyloid plaque score**

- **Sup. Frontal**
- **Sup. Parietal**
- **Occipital**
- **Inf. Temporal**
PiB retention accurately detects neuritic Aβ plaques in Lewy body diseases

PiB retention is low when Aβ is sparse and increases when Aβ is deemed moderate or extensive. Of the 4 cases with the lowest PiB SUVR (the open diamonds), 2 were cognitively normal at the time of imaging and 2 were classified as PD-MCI; the median interval between imaging and death in these 4 was 6 years compared to the overall median of 4 years.

*Filled circles = DLB*
*Open diamonds = PD-MCI*

**A**

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<th>PiB (SUVR)</th>
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<td>1.4</td>
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*r = 0.59, p = 0.01*

**B**

<table>
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<th>PiB (SUVR)</th>
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<tr>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>3</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*r = 0.45, p = 0.07*
60 year old man with DLB, MMSE = 21, Braak Lewy body stage 4, with no Aβ deposits and no PiB uptake
75 year old man with DLB, Braak stage 6, MMSE = 17, with high PiB uptake and plentiful Aβ plaques.
PiB retention correlated significantly with both Braak NFT (A) and Lewy body (B) scores

\[ r = 0.68, \ p = 0.004 \]
\[ r = 0.54, \ p = 0.03 \]

Filled circles = DLB
Open diamonds = PD-MCI
PDD

-Shirvan.....Gomperts. Neurology 93:476-484, 2019
Conclusions

• PiB amyloid, AV-1451 tau and Altropane DAT brain scans are useful biomarkers in characterizing DLB/PDD and distinguishing these Lewy body dementias from other dementing illnesses, such as AD.

• These biomarkers accurately detect in life the Lewy body dementia spectrum of molecular pathologies.

• Detecting increased Aβ and/or neurofibrillary tangles in Lewy body diseases suggests commonalities in the pathogenesis of dementing illnesses. When effective treatments directed against these lesions are confirmed in AD, these treatments should be directed toward the Lewy body dementias as well.
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Joe Locascio, Rong Ye & Julia Shirvan – Data management & statistics
Keith Johnson – Neuroimaging
Bradford Dickson – Neurology & neuroimaging
Steve Gomperts – Neurology; PI, LBDA Center of Excellence at MGH
Dorene Rentz - Neuropsychology

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