The Lewy body dementias: Dementia in Parkinson’s disease and dementia with Lewy bodies

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«He died from suicide in 2014 at the end of an intense, confusing, and relatively swift persecution at the hand of the disease»

«Not until the coroner’s report, 3 months after his death, would I learn that it was diffuse DLB that took him»

«He had been struggling by symptoms that seemed unrelated: constipation, urinaty difficulty, heartburn, insomnia, poor sense of smell- and a lot of stress»

«His fear and anxiety skyrocked…..panick attacks- antipsychotics

«Doctor appointments, psychiatrist, testing, and examinations kept us in constant motion»

«It felt like he was drowning in symptoms- and I was drowning along with him»
Key clinical challenges:

Diagnose cognitive impairment and dementia in PD
Distinguish DLB from Alzheimer’s disease
Management of DLB and PDD

Less important: Distinguish PDD from DLB
Frequency of dementia in PD

Point-prevalence: 25-30%

Cumulative prevalence 80%

The Sydney Study. Hely et al. 2008
## How common is PD-MCI?

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>%MCI</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pai et al 2001</td>
<td>102</td>
<td>38.2</td>
<td>Clinic</td>
</tr>
<tr>
<td>Foltynie et al 2004</td>
<td>146</td>
<td>30.1</td>
<td>Community/Incidence</td>
</tr>
<tr>
<td>Muslimovic et al 2005</td>
<td>115</td>
<td>23.5</td>
<td>Clinic(early PD)</td>
</tr>
<tr>
<td>Hoops et al 2009</td>
<td>115</td>
<td>17.4</td>
<td>Clinic</td>
</tr>
<tr>
<td>Aarsland 2009</td>
<td>196</td>
<td>18.9</td>
<td>Community/Incidence</td>
</tr>
<tr>
<td>Mamikonyan et al 2009</td>
<td>106</td>
<td>29.2%</td>
<td>Clinic</td>
</tr>
</tbody>
</table>

### MCI in PD

<table>
<thead>
<tr>
<th>Reference</th>
<th>N PD/NCI</th>
<th>Selection</th>
<th>Age</th>
<th>Cut-off</th>
<th>Definition impaired</th>
<th>Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reid et al 1996</td>
<td>91/50</td>
<td>Hospital</td>
<td>63</td>
<td>2 SD</td>
<td>“Dem”</td>
<td>17%</td>
</tr>
<tr>
<td>Muslimovic 05</td>
<td>115/70</td>
<td>Hospital</td>
<td>66.2</td>
<td>2 SD</td>
<td>3/17</td>
<td>PD: 24%</td>
</tr>
<tr>
<td>Foltynie 2004</td>
<td>159/no</td>
<td>Incidence</td>
<td>70.6</td>
<td>1 SD</td>
<td>1/3</td>
<td>36%</td>
</tr>
<tr>
<td>Aarsland 2008</td>
<td>196/175</td>
<td>Incidence</td>
<td>67.6</td>
<td>1.5</td>
<td>1/3</td>
<td>PD: 18.9%</td>
</tr>
<tr>
<td>Elgh 2009</td>
<td>88/30</td>
<td>Community</td>
<td>68</td>
<td>1.5</td>
<td>1/5 domains</td>
<td>30%</td>
</tr>
<tr>
<td>Yarnall 2014</td>
<td>219</td>
<td>Incidence</td>
<td>66</td>
<td>1.5</td>
<td>MDS</td>
<td>42.5%</td>
</tr>
</tbody>
</table>
Diagnosis and management of dementia with Lewy bodies
Fourth consensus report of the DLB Consortium

McKeith et al
Online June 8th, 2017
(Open access)
Clinical features:

Core features:
- Fluctuating cognition
- Visual hallucinations
- REM sleep behavior disorder
- Parkinsonian features

Supportive features:
- Severe sensivity to antipsychotics
- Postural instability
- Repeated falls
- Syncope
- Severe autonomic dysfunction
- Hallucinations in other modalities
- Delusions
- Apathy, anxiety, and depression
Biomarkers:

**Indicative markers:**

- Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
- Abnormal (low uptake) 123iodine-MIBG myocardial scintigraphy.
- Polysomnographic confirmation of REM sleep without atonia.

**Supportive markers:**

- Relative preservation of medial temporal lobe structures on CT/MRI scan.
- Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity in the cingulate island sign on FDG-PET imaging.
- Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.
**Diagnosis:**

**Probable DLB**

a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or

b. Only one core clinical feature is present, but with one or more indicative biomarkers.

Probable DLB should NOT be diagnosed on the basis of biomarkers alone.

**Possible DLB**

a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or

b. One or more indicative biomarkers is present but there are no core clinical features.
The prognosis of dementia with Lewy bodies

Christoph Mueller, Clive Ballard, Anne Corbett, Dag Aarsland

Lancet Neurol 2017
Prognosis of DLB:

Time to nursing home admission

Rongve 2014
How to diagnose DLB
Misdiagnosis of DLB: LBDA Web-based survey of 962 DLB carers

Number of doctors visited before diagnosis:
- 1: 7.6%
- 2: 25.3%
- 3: 28.4%
- 4: 18.6%
- 5: 5.6%
- >5: 14.7%

Time from first visit to diagnosis:
- At first visit - 9.3%
- Within one week - 1.6%
- One month - 8.3%
- 3 months - 8.3%
- 6 months - 11.3%
- 12 months - 11.7%

Galvin et al 2010
Remember: DLB is a common dementia diagnosis

Active use of DLB diagnostic criteria

Screen all dementia patients for DLB:
- Visual hallucinations?
- Fluctuation cognition?
- Parkinsonism?
- REM-sleep behavioral disorder?
- Cognitive profile?

If suspect DLB: Use biomarkers
- Dopamine transporter SPECT or PET
- Cardiac SPECT (MIBG)
- EEG
### Table 1
Lewy body composite risk score

<table>
<thead>
<tr>
<th>Does the patient…</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?</td>
<td></td>
<td></td>
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<tr>
<td>Have rigidity (with or without cogwheeling) on passive range of motion in any of the 4 extremities?</td>
<td></td>
<td></td>
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<tr>
<td>Have a loss of postural stability (balance) with or without frequent falls?</td>
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<td></td>
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<tr>
<td>Have a tremor at rest in any of the 4 extremities or head?</td>
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<td></td>
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<tr>
<td>Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?</td>
<td></td>
<td></td>
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<tr>
<td>Have episodes of illogical thinking or incoherent, random thoughts?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have frequent staring spells or periods of blank looks?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have visual hallucinations (see things not really there)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appear to act out his/her dreams (kick, punch, thrash, shout or scream)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have orthostatic hypotension or other signs of autonomic insufficiency?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cognitive Impairment: MoCA, ACE, MMSE
Visual hallucinations: Neuropsychiatric Inventory
Fluctuation cognition: Mayo fluctuation scale
Parkinsonism: UPDRS motor subscale
REM-sleep behavioral disorder: Mayo Sleep scale
Cardiac MIBG SPECT (Heart/mediastinum uptake ratio)

Figure 2  
$^{123}$Iodine-metaiodobenzylguanidine myocardial imaging in patients with Alzheimer disease (AD), dementia with Lewy bodies (DLB), and age-matched normal controls (NC)

AD

DLB

NC

3.94  1.34  3.44

H/M ratio
FDG-PET: Preserved occipital metabolism; cingulate island sign

Figure 4. $^{18}$F-FDG-PET images in Alzheimer disease (AD), dementia with Lewy bodies (DLB), and normal controls (NC).
European DLB consortium: E-DLB

Retrospective analysis of longitudinal data

25 centers from 13 European countries and one in the US

Data collection period: 2000 to 2016

Prospective data collection ongoing
CSF-AD profile is common and predicts rapid cognitive decline

CSF AD profile* is common in DLB (46%)

Low CSF abeta42 (RED) predicts more rapid cognitive decline in DLB

* tau/aβ42 >0.52 (Duits 2014).

Mean difference: 2.9, p<.01

Steenoven I et al. JAD 2015

Abdelnour et al Mov Disord 2016
A diagnosis of DLB/PDD should lead to:

- Information about disease, explanation, prognosis
- Careful drug review
- Non-pharmacological strategies (VH coping, sleep hygiene, strategies against autonomous symptoms)
- Considering symptomatic drug treatment
  - ChEIs-base treatment
  - Psychotropics? Antipsychotics?? Clozapine under-used!
  - Autonomous symptoms
  - Antiparkinson
- Careful monitoring in specialist centre
Management of DLB/PDD in clinical practice

Challenges
- Many different symptoms
- Treating one symptom may worsen another
- High risk for side-effects
- Robust evidence lacking

Strategy
- Discuss with patient/family which symptom to target first
- Treatment benefit/adverse events need to be carefully monitored
- Cholinesterase inhibitors as base treatment
The Lewy body dementias at IOPPN/SLAM

SLAM:

Parkinson Spectrum Memory Clinic
Clinic-based research:
CRIS
Planned service-based intervention
Collaboration with Neurology and Geriatrics
KHP Dementia Strategy-CSF Trials (Axovant, GE)

IOPPN:

-synaptic pathology in PD/DLB
-GBA program: animal and iPSC-CSF-based biomarkers
-2 PET studies
-Drug-development (SMART-PD)- repurposing
-Cohort biomarker study
Summary & Conclusions

- Cognitive impairment common in PD
- PD and DLB share pathologic and clinical features
- DLB is common but frequently misdiagnosed
- Management challenging but treatment options exits
- New clinical translational research area at IOPPN/SLAM