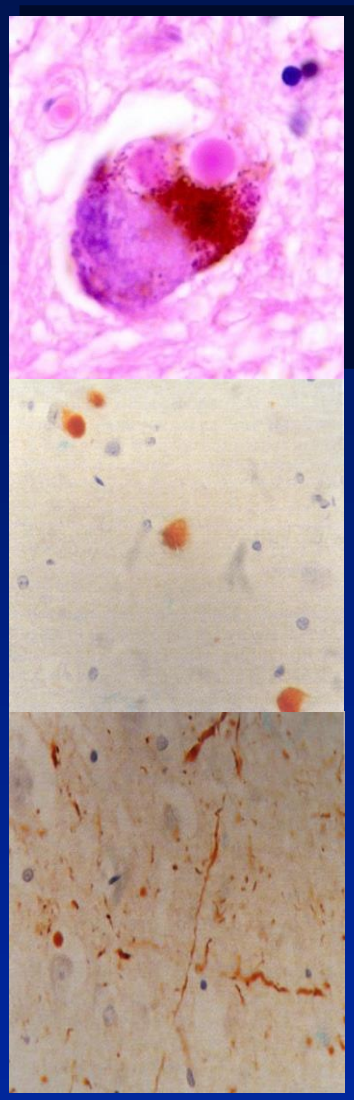
How to Diagnose Early (Prodromal) Lewy Body Dementia

Ian McKeith MD, FRCPsych, F Med Sci.



Lewy Body Disease

Time

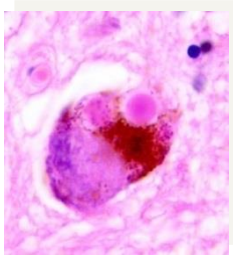
Parkinson's Disease

PD Dementia

Dementia with Lewy Bodies (DLB)

Lewy Body Dementias

Diagnostic Criteria for DLB



McKeith et al, Neurology, 2005

- **Cognitive decline & reduced social/occupational function**
  - Attentional, executive and visuo-spatial dysfunction prominent
- **CORE features**
  - Fluctuation
  - Recurrent visual hallucinations
  - Spontaneous parkinsonism
- **Suggestive features**
  - REM sleep behaviour disorder
  - Neuroleptic sensitivity
  - Dopaminergic abnormalities in basal ganglia on SPECT/PET

At least one core + one suggestive or 2 core features for Probable DLB

One core or suggestive feature sufficient for Possible DLB

Lewy Body Dementia (DLB and PDD)

- Estimated 4M people affected worldwide

- **Diagnostic criteria agreed globally for**
- PD (1992)
- DLB (1996/2005)
- PDD (2007)
- PD-MCI (2012)

- **LBDs are now included in DSM V (2013)**

- Neurocognitive disorder with Lewy bodies

- Neurocognitive disorder due to Parkinson's disease

Typical DLB

Atypical DLB

Biomarker

Typical DLB

Prodromal DLB

Atypical DLB

Biomarker

Prodromal DLB

- An emerging definition of prodromal DLB might follow the model of prodromal AD
- i.e. a relevant clinical deficit
  - Cognitive
  - Neuropsychiatric
- plus a disease specific biomarker
  - Neuroimaging
  - CSF / blood
  - Genes
  - Tissue biopsy

Retrospective Survey of Prodromal Symptoms in Dementia with Lewy Bodies: Comparison with Alzheimer's Disease

Chiba et al, Dem Ger Cog Dis 2012

Table 3. Prevalence of non-motor symptoms of PD in subjects

	DLB patients (n = 34)	AD patients (n = 32)	Normal controls (n = 30)
Cognitive impairment			
Memory loss	34 (100)[a]	32 (100.0)[a]	14 (46.7)
X Anosmia or hyposmia	14 (41.1)[a, b]	2 (6.2)	2 (6.7)
Autonomic dysfunction			
X Constipation	16 (47.1)[a, b]	5 (15.6)	5 (16.7)
Orthostatic dizziness	8 (23.5)[b]	0 (0)	1 (3.3)
Urinary incontinence	9 (26.5)	3 (9.4)	2 (6.7)
Increased sweating	5 (14.7)	1 (3.1)	4 (13.3)
Increased saliva	7 (20.6)[a, b]	0 (0)	0 (0)
Sleep disturbance			
Sleep rhythm change	21 (61.8)[a, b]	1 (3.1)[a]	8 (26.7)
X Crying or shouting	21 (61.8)[a, b]	2 (6.3)	1 (3.3)
Limb movements	12 (35.3)[a, b]	0 (0)	2 (6.7)
Nightmares	9 (26.5)[a, b]	0 (0)	1 (3.3)
Psychiatric symptoms			
Depression	8 (23.5)[a]	3 (9.4)	0 (0)
Anxiety	9 (26.4)[b]	1 (3.1)	2 (6.7)
Moodiness	4 (11.8)	3 (9.4)	0 (0)
Lack of motivation	9 (26.4)[a]	6 (18.8)[a]	0 (0)

Patients and carer asked to complete a 15 item checklist of NMS of PD at first attendance to Memory Clinic

No of Symptoms	Sens %	Spec %
1	71	81
2	38	97
3	15	100

Sequence of clinical symptoms/signs

Symptom	% with onset before/with memory impairment	Average onset relative to memory impairment (yrs)
Constipation	57	-13.1
Decreased sense of smell	38	-12.4
REM sleep behaviour disorder	46	-7.8
Dizziness on standing	18	-4.5
Parkinsonism	31	-0.3
Visual Hallucinations	31	-0.4

Fujishiro et al. *Psychogeriatrics* 2013; 13:128-38

RBD, hyposmia and autonomic dysfunction alone or together will predict LB disease not DLB.

The same will likely be true of "early" biomarkers

Once a patient has extrapyramidal symptoms or cognitive decline they can probably be regarded as differentiated into either early PD or early DLB

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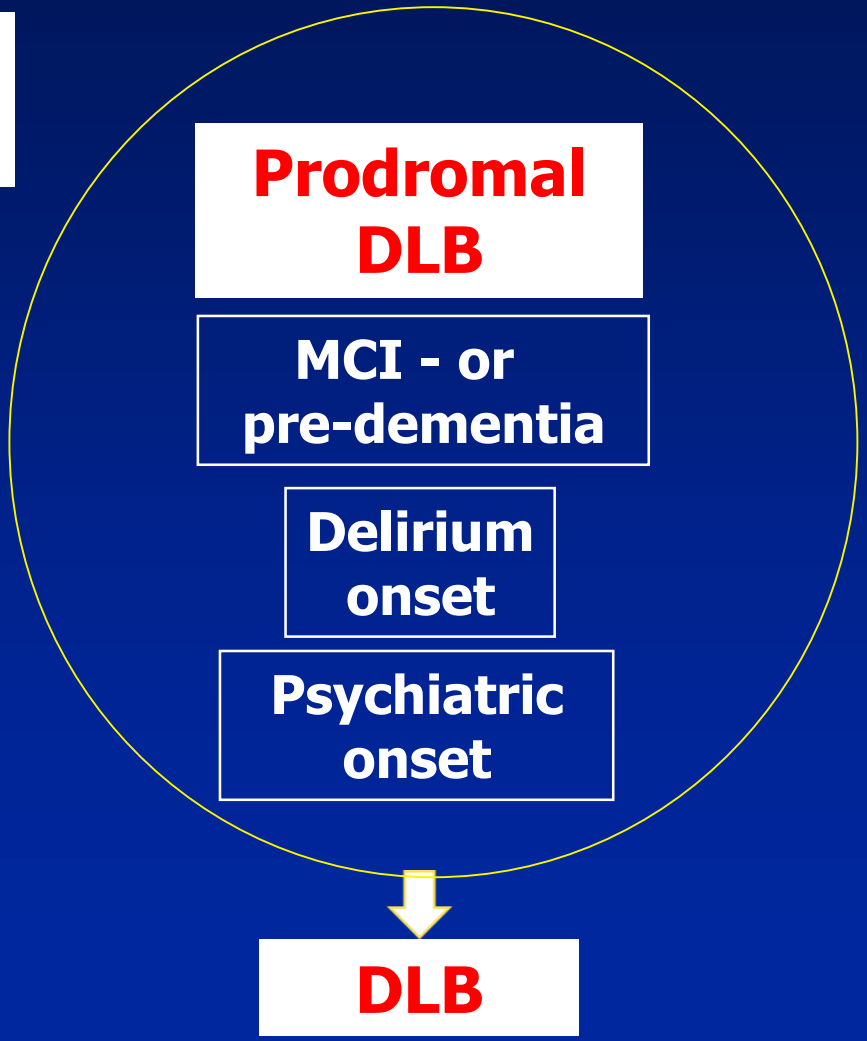

Nonamnestic mild cognitive impairment progresses to dementia with Lewy bodies

Ferman et al:

Neurology® 2013;81:2032-2038

	327 MCI			
	278 Amnestic MCI		49 Nonamnestic MCI	
	245 Single-domain amnestic MCI	33 Multidomain amnestic MCI	38 Single-domain nonamnestic MCI	11 Multidomain nonamnestic MCI
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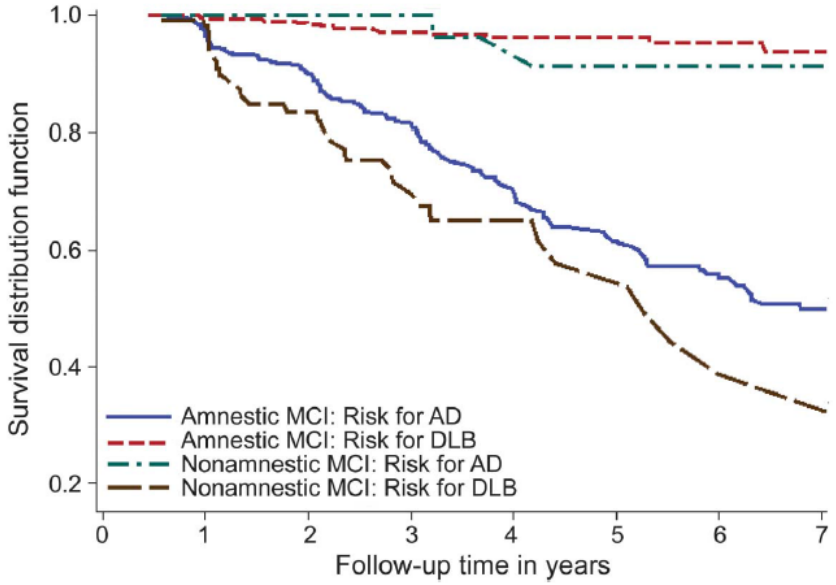
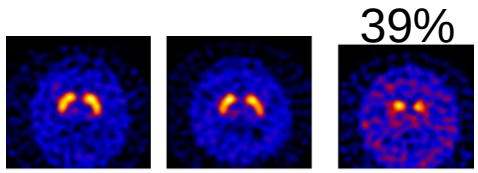
Stable MCI	98	5	11	2

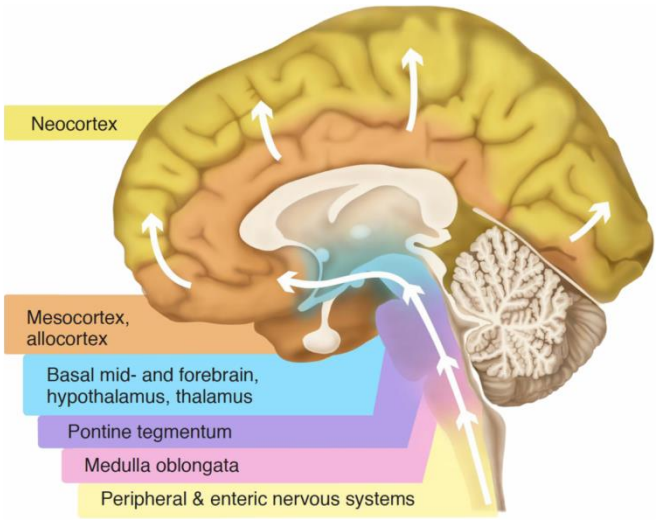


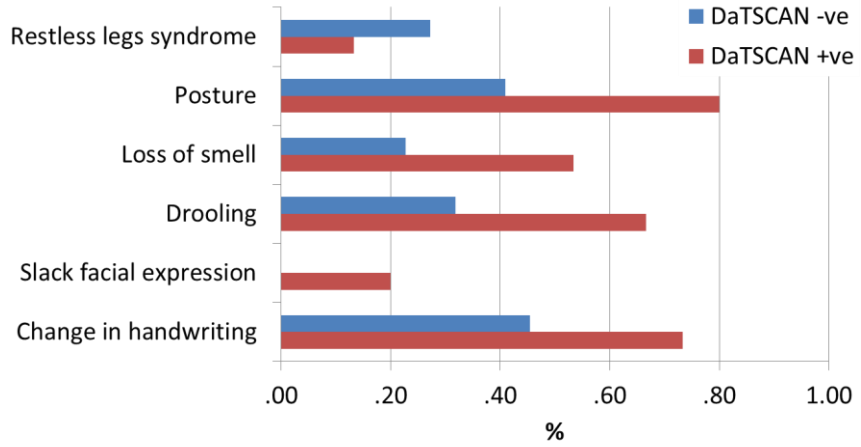
At baseline, 80% of MCI who developed probable DLB had RBD vs 8% who developed probable AD

MCI ➡ DLB also more likely to have baseline fluctuations, daytime sleepiness and subtle but measurable extrapyramidal signs

Prodromal DLB

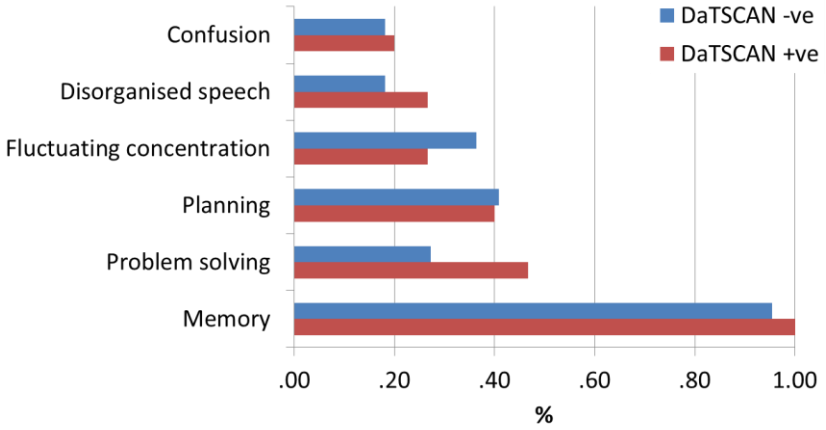






The LewyPro Study

100 subjects with MCI and a symptom of Lewy body disease
e.g. visual hallucinations, parkinsonism, cognitive fluctuations, RBD
Deep and frequent phenotyping approach

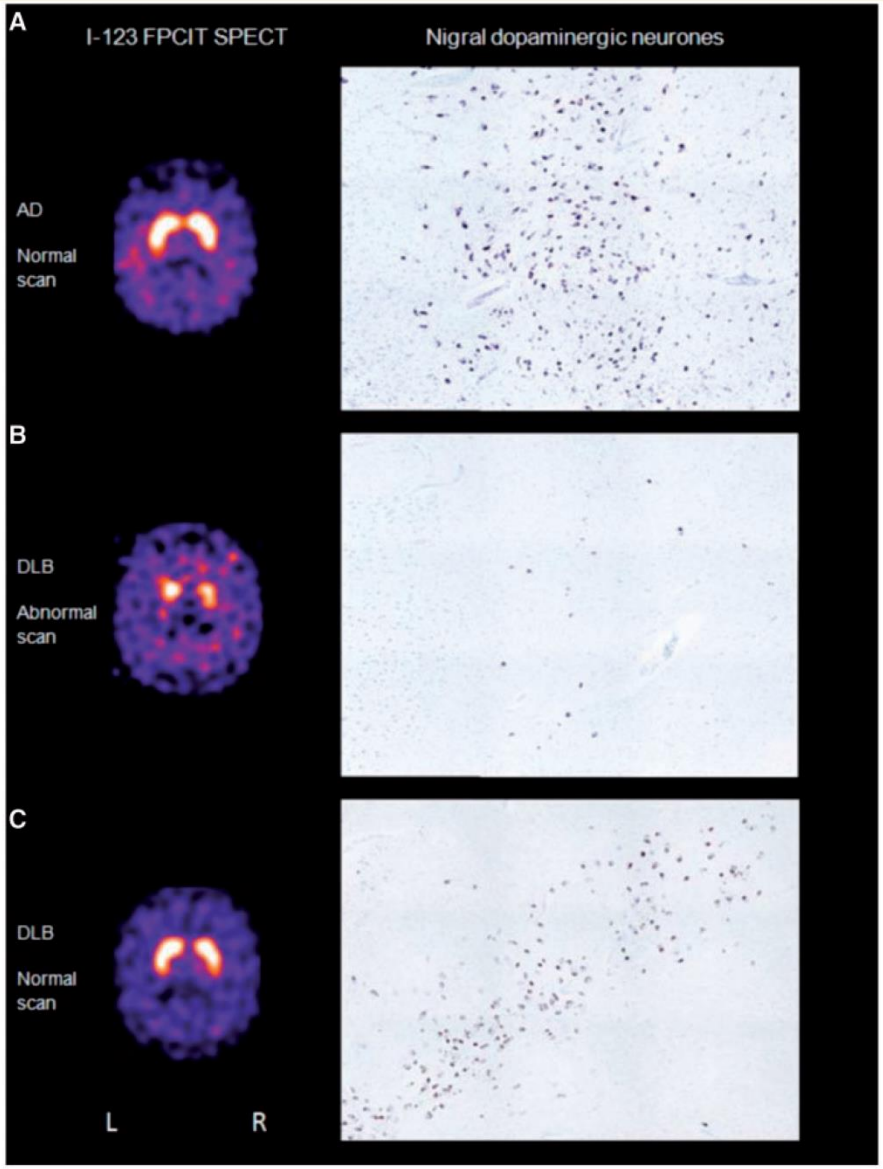


Newcastle University
Newcastle Hospitals NHS Foundation Trust

Newcastle Biomedical Research Unit

NHS National Institute for Health Research

Illustration: Visanji et al. *Acta Neuropathol Commun* 2013; 1:2



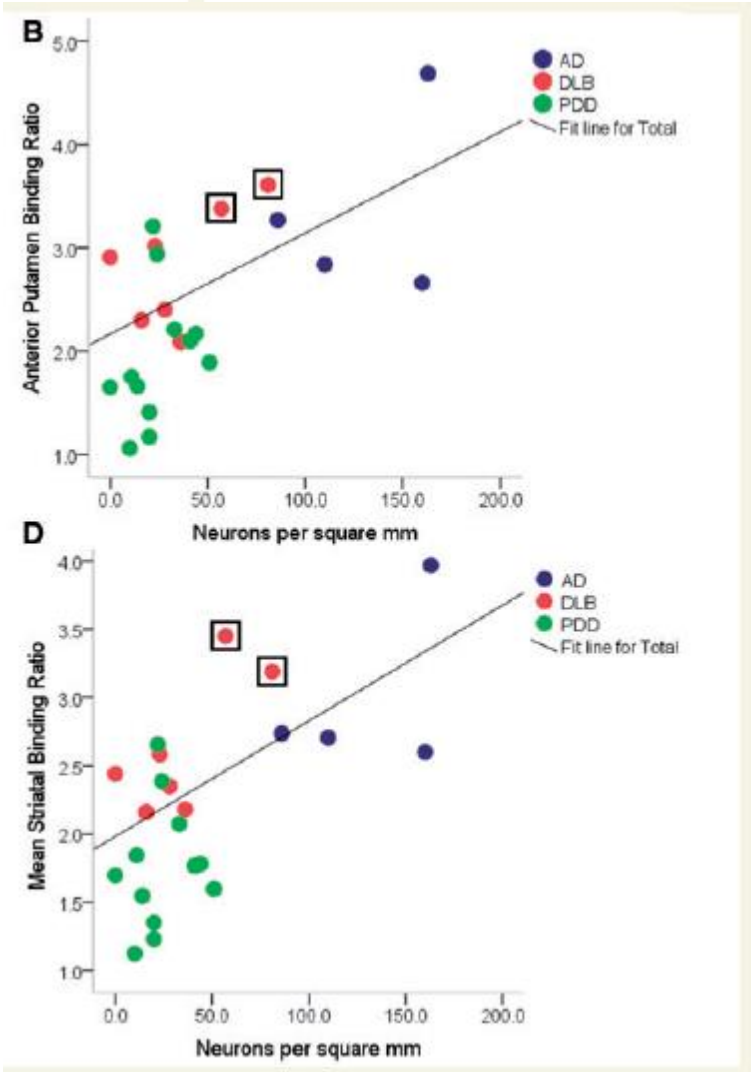
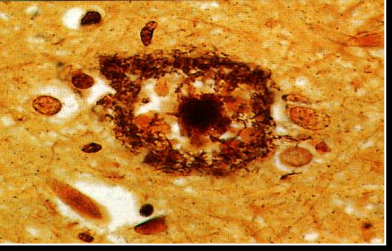
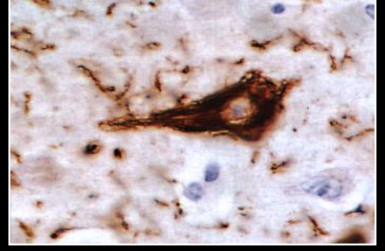
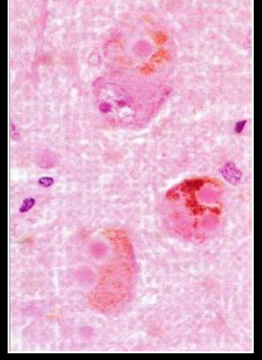


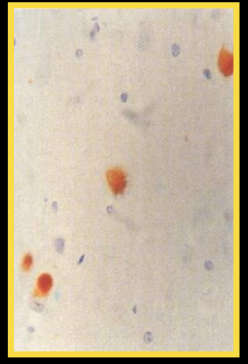
Figure 4 Axial ^{123}I-FP-CIT SPECT scans with corresponding images of nigral dopaminergic neurons. (**A**) Subject with Alzheimer's disease (AD) with a 'grade 0—normal' FP-CIT scan and nigral density of 160 neurons per mm^2. (**B**) Subject with dementia with Lewy bodies (DLB) with a 'grade 2—abnormal' FP-CIT scan and nigral density of 16 neurons per mm^2. (**C**) Subject with dementia with Lewy bodies with a 'grade 0—normal' FP-CIT scan and nigral density of 81 neurons per mm^2. Note, FP-CIT SPECT scans are displayed neurologically (left on left side, L = left, R = right).



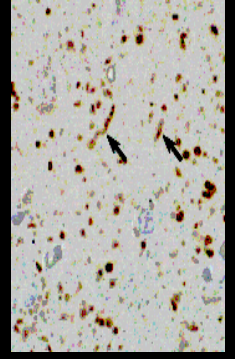


Alzheimer pathology

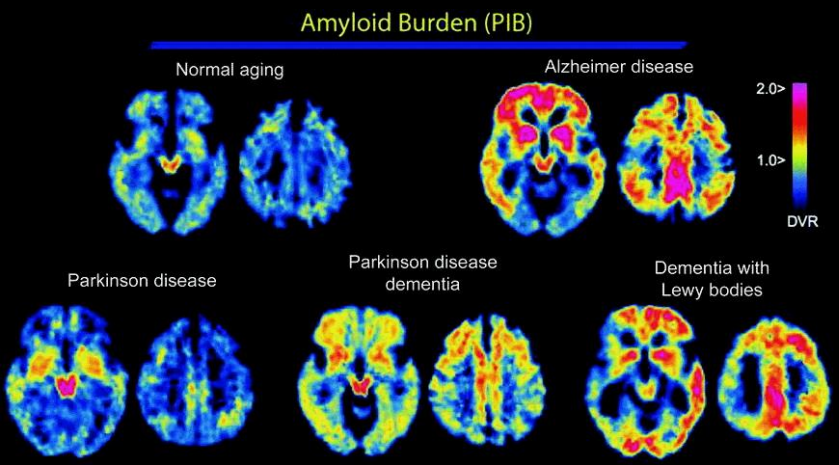




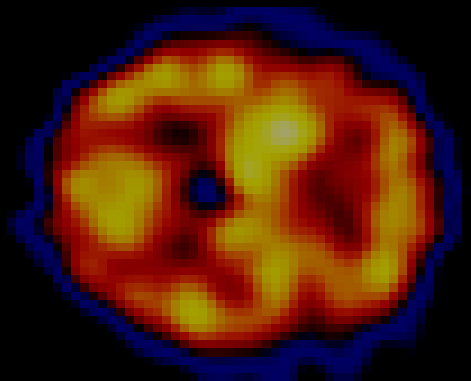
Lewy bodies

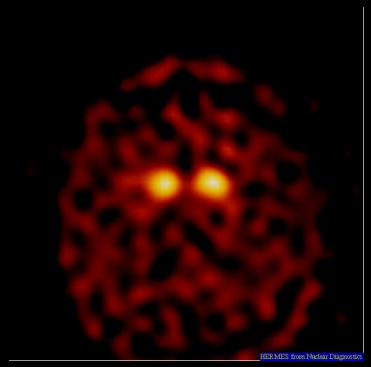


Lewy neurites



LBD biomarkers have so far been developed for mid course diagnosis, not for early disease or progression





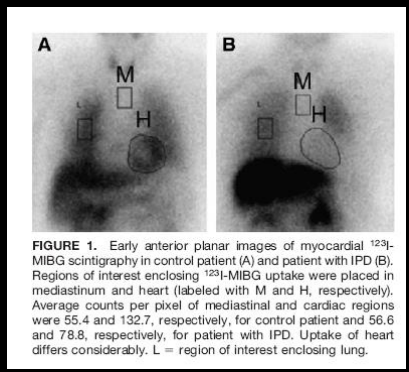
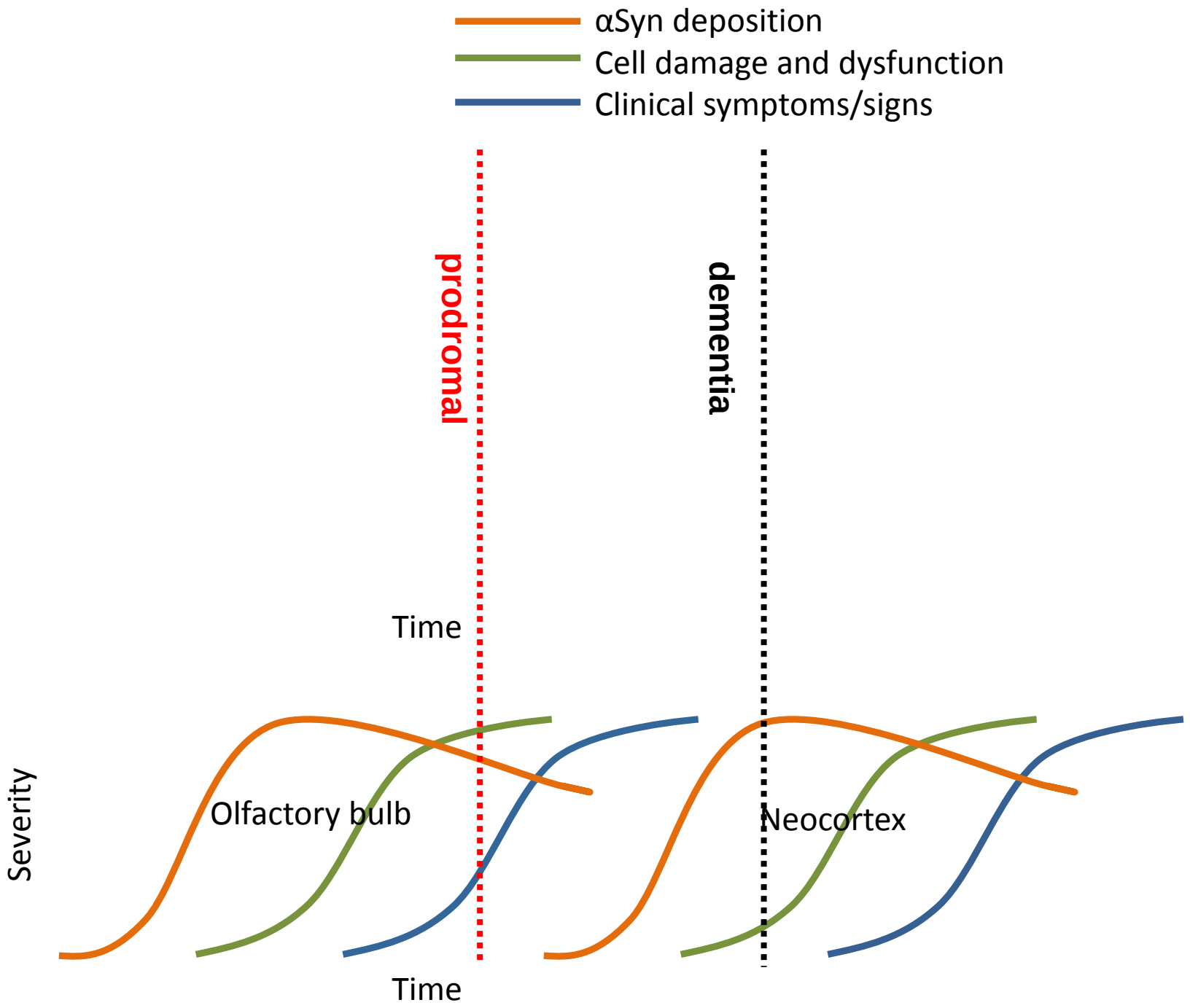


FIGURE 1. Early anterior planar images of myocardial ^{123}I-MIBG scintigraphy in control patient (A) and patient with IPD (B). Regions of interest enclosing ^{123}I-MIBG uptake were placed in mediastinum and heart (labeled with M and H, respectively). Average counts per pixel of mediastinal and cardiac regions were 55.4 and 132.7, respectively, for control patient and 56.6 and 78.8, respectively, for patient with IPD. Uptake of heart differs considerably. L = region of interest enclosing lung.

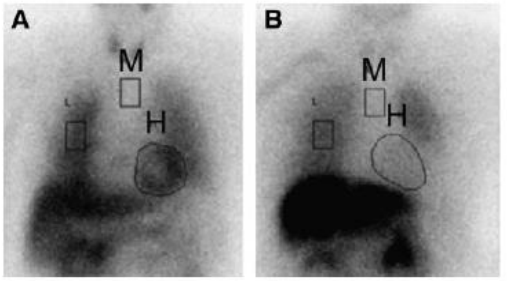

αSyn deposition
Cell damage and dysfunction
Clinical symptoms/signs
prodromal
dementia
Time
Severity
Olfactory bulb
Neocortex
Time

Autonomic nervous system biopsy as an early diagnostic marker for LB disease

- 28/28 PD autopsy cases had α-synuclein in submandibular gland (Adler et al, 2013) – preliminary data suggest 9/11 positive needle biopsies in-vivo

- α-synuclein positive sub-mucosal biopsies from sigmoid colon (Pouctet et al, 2012) and cutaneous autonomic nerves (Wang et al, 2013) in PD

- Multiple reports of abnormal scintigraphy in DLB – cardiac sympathetic innervation



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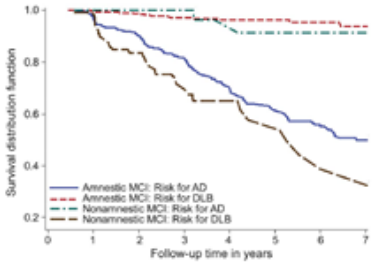

At baseline, 80% of MCI who developed probable DLB had RBD vs 8% who developed probable AD

MCI ➡ DLB also more likely to have baseline fluctuations, daytime sleepiness and subtle but measurable extrapyramidal signs

In the absence of evidence the current challenge is managing patients with suspected prodromal DLB -

- pre-dementia
- delirium
- psychiatric

Tell patient and family

Avoid neuroleptics

Early use of CHEIs ?

Multisystem review

PROSPERO International prospective register of systematic reviews

A systematic review of management strategies for Lewy body dementia (dementia with Lewy bodies and Parkinson's disease dementia)

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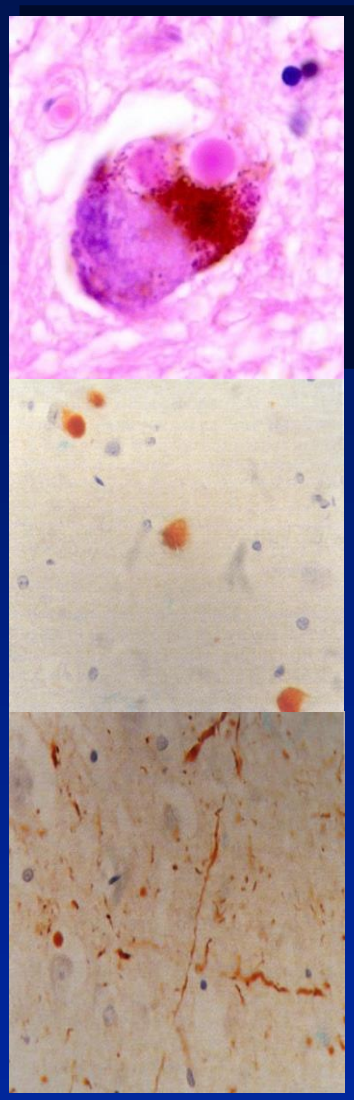
"From the 27,956 unique hits there were a dozen papers on prodromal DLB, none of which were about management. The closest is a transcranial magnetic stimulation for depression in 'suspected' (the authors' criteria) DLB."



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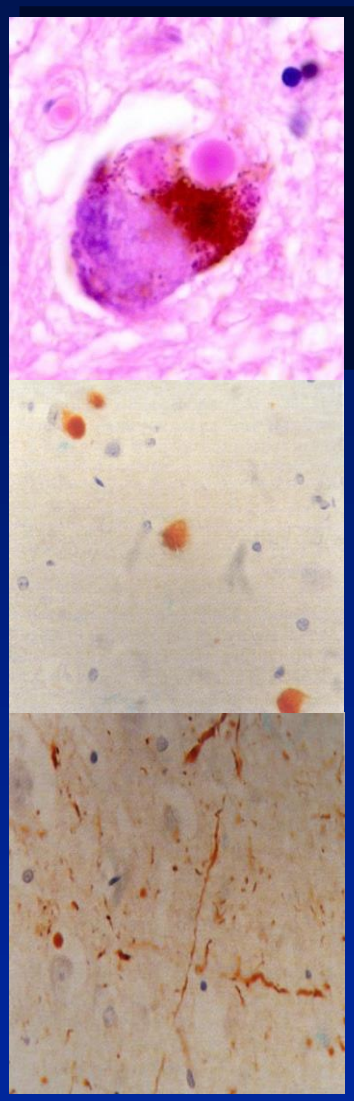
Lewy Body Dementias



Prodromal

Lewy Body Disease

Prodromal
Parkinson's Disease

Mild Cognitive Impairment (MCI)

PD Dementia

Prodromal
Dementia with Lewy Bodies (DLB)

Time

Lewy Body Dementias

Prodromal DLB

- Will be clinically heterogeneous
  - Pre-dementia
  - Delirium
  - Psychiatric
- No criteria for prodromal DLB exist yet
- Several prospective cohorts already established
- Unclear which biomarkers will be sensitive early in disease

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- Will be clinically heterogeneous
- No criteria for prodromal DLB exist yet
- Several prospective cohorts already established
- Unclear which biomarkers will be sensitive early in disease
- Prodromal symptoms are currently most useful to help establish the subtype diagnosis in established cases of dementia

6th International Conference on DLB

Tuesday December 1 through Friday December 4, 2015

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