Diagnostic process in Lewy body disease:
the role of assessment tools and biomarkers

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400,000 men and women across the US were involved in the Apollo programme.

support of over 20,000 industrial firms and universities.
We are working to END dementia

IT TAKES A VILLAGE
Outline

A Lewy body disease definition

B Current diagnostic tools and biomarkers

C Future diagnostic tools in LBD
Lewy body disease definition
Continuum

- Parkinson's disease
  - Parkinson's disease MCI
    - Parkinson's disease dementia
      - Prodromal stage of dementia with Lewy bodies
        - Dementia with Lewy bodies
  - Dementia with Lewy bodies

Lewy body disease
 Deposits of α-synuclein

A) Lewy body in a neuron of the substantia nigra, B) in a pyramidal cell of CA1 area of the hippocampus, and C) in cingulated cortex (C) (arrows). Lewy body (arrow) and Lewy neurites (arrowheads) in the substantia nigra (D). Cortical Lewy bodies (E,F). (A–C) hematoxylin–eosin; (D–F) anti-α-synuclein immunostaining.

Taipa R et al. Front Neurol. 2019
Dementia occurs before or concurrently with parkinsonism

Dementia occurs in the context of well-established Parkinson’s disease

**Fourth consensus criteria for probable and possible dementia with Lewy bodies**

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<tr>
<th>Essential</th>
<th>Clinical features</th>
<th>Biomarkers</th>
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<td>Recurrent visual hallucinations</td>
<td>Decreased dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET</td>
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<td>Core</td>
<td>Fluctuating cognition</td>
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<td>REM sleep behavior disorder</td>
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<td>One or more spontaneous cardinal features of parkinsonism: bradykinesia, rest tremor or rigidity</td>
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<td>Severe sensitivity to antipsychotic agents</td>
<td>Relative preservation of medial temporal lobe structures on CT/MRI</td>
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<td>Supportive</td>
<td>Postural instability</td>
<td>Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity +/- the cingulate island sign on FDG-PET</td>
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<td>Syncope or other transient episodes of unresponsiveness</td>
<td>Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range</td>
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<td>Systematized delusions</td>
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<td>Hallucinations in other modalities</td>
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<td>Repeated falls</td>
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<td>Severe autonomic dysfunction</td>
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<td>Hypersomnia</td>
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<td>Apathy, anxiety and depression</td>
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<td>Hyposmia</td>
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**Criteria for diagnosis of probable and possible PD-D**

**Probable PD-D**

I. Core features: both must be present
   - Diagnosis of Parkinson’s disease according to Queen Square Brain Bank criteria.
   - A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson’s disease and diagnosed by history, clinical, and mental examination.

II. Associated clinical features:
   - Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
   - The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis.

III. Features which do not exclude PD-D, but make the diagnosis uncertain:
   - Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging.
   - Time interval between the development of motor and cognitive symptoms not known.

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D.

**Possible PD-D**

I. Core features: both most be present

II. Associated clinical features:
   - Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention.
   - Behavioral symptoms may or may not be present.

OR

I. One or more of the group III features present.

II. None of the group IV features present.
What is the difference between Parkinson’s disease dementia and Dementia with Lewy bodies?
Current diagnostic tools and biomarkers in LBD
**Why is important to diagnose LBD?**

**Second** most common cause of neurodegenerative dementia after Alzheimer’s disease.

**Underdiagnosed** disease

Prevalence:
- 4.2-4.6% community
- 7.5% secondary care
- 20% neuropathological diagnosis

**Worse** health indicators

↑ Mortality
↑ Functional impairment
↑ Impact in quality of life
↑ Healthcare costs
Earlier nursing home admission
↑ Rates of hospitalization

Heidenbrink JL et al. J Geriatr Psychiatry Neurol. 2002
Aarsland D et al. Dement Geriatr Cogn Disord. 2008
Vann Jones S et al. Psychol Med. 2014
Outeiro TF et al. Mol Neurodegener. 2019
Mueller C et al. Lancet Neurol. 2017
Profile of cognitive impairment in Lewy body disease

Cognitive impairment

- Executive function
- Visuospatial function
- Attention and working memory
- Language
- Memory
Current biomarkers in Lewy body disease

Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET

Relative preservation of medial temporal lobe on CT/MRI

McKeith I et al. Neurology, 2017
Current biomarkers in Lewy body disease

Generalized low uptake on SPECT/PET perfusion/metabolism scan, reduced occipital activity

The posterior **cingulate island sign** on FDG-PET imaging

Abnormal (low-uptake) in $^{123}$Iodine-metaiodobenzylguanidine myocardial imaging (MIBG)

McKeith I et al. *Neurology*, 2017
Polysomnography confirmation of REM sleep without atonia.

PSG recordings of normal REM sleep

REM sleep without atonia, typical of REM sleep behavior disorder

Prominent posterior slow-wave EEG activity with periodic fluctuations in the pre-alpha/theta range
Future diagnostic tools in LBD
Biomarkers for Lewy body disease

Where?

Blood
Cerebrospinal fluid
Skin
Submandibular gland
Saliva
Olfactory mucosa
Biomarkers for Lewy body disease

Where?
- Blood
- Cerebrospinal fluid
- Skin
- Submandibular gland
- Saliva
- Olfactory mucosa
Biomarkers for Lewy body disease

Alpha-synuclein Positron Emission Tomography

Control, 52

Control, 69

MSA-C, 55

MSA-C, 63

SUVR

0.0 4.0
Identifying co-pathologies
Co-pathologies in Lewy body disease

- 10-20% "Pure" cases
- ~50% Lewy + Alzheimer
- 30% Lewy + vascular
Digital biomarkers

Sensing from the IoT behavioral variables: "indirect" digital biomarker

Psychological and medical diagnostics without biological variables (behavioral assessments)

Person interacts with the Internet of Things

Person takes a (behavioral) test

From these test results a clinical outcome and underlying biology might be sensed

Sensing from the IoT biological variables of a person: "direct" digital biomarker

Montag et al. Front. Psychiatry. 2021
1. **Lewy body disease = dementia with Lewy bodies and Parkinson’s disease dementia.**
   - Etiology: deposits of alpha-synuclein (*Lewy bodies* and *Lewy neurites*).
   - The difference between these two diseases relies on what symptom presented first: cognitive or motor?
     - Dementia with Lewy bodies: dementia occurs before or concurrently with parkinsonism.
     - Parkinson disease dementia: dementia occurs in the context of well-established Parkinson’s disease.

2. **Current diagnostic tools include:** comprehensive neuropsychological examination, MRI, dopamine transporter SPECT or PET, MIBG, PSG, FDG-PET, and EEG.

3. **Future diagnostic tools:** biofluid biomarkers, alpha-synuclein tracers, digital biomarkers.
“We choose to go to the Moon!

We choose to go to the Moon... We choose to go to the Moon in this decade and do the other things, not because they are easy, but because they are hard; because that goal will serve to organize and measure the best of our energies and skills, because that challenge is one that we are willing to accept, one we are unwilling to postpone, and one we intend to win, and the others, too.”

John F. Kennedy

We choose to END dementia!