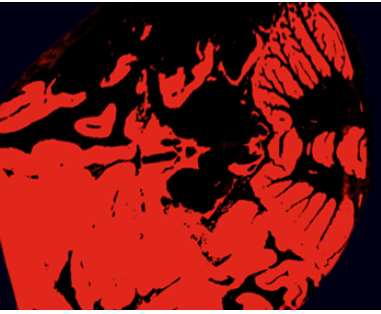
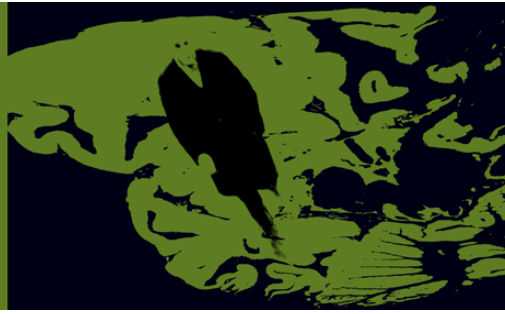


BRAINWEEK™ twenty 21 | Live Virtual Conference | MAY 7–9



Diagnosing on the Spectrum: Alzheimer's Disease and Lewy Body Dementia

Yasar Torres-Yaghi, MD

Associate Professor of Neurology

Georgetown University Medical Center

Disclosure

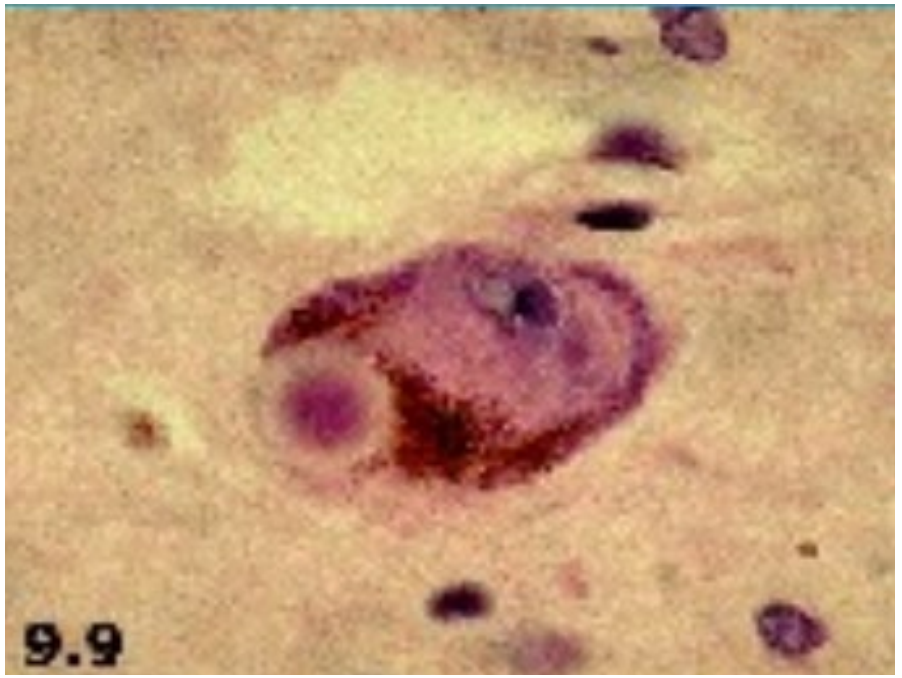
- Consulting Fee (e.g., Advisory Board): AbbVie, Abbott, Acorda, Amneal, Medtronic, Acadia, Adamas, USWORLDMEDS, Biogen
- Speakers' Bureau: AbbVie,Abbott, Acorda, Amneal, Medtronic, Acadia, Adamas, USWorldMeds, Biogen

Learning Objectives

- Differentiate Lewy body dementia (LBD) and dementia with Lewy bodies (DLB)
- Explain the neuropathology of LBD/DLB
- Outline the protocol for LBD/DLB diagnosis
- Describe core symptoms and supporting clinical features of LBD/DLB
- List available medications to treat symptoms of LBD/DLB
- Discuss current research on LBD/DLB

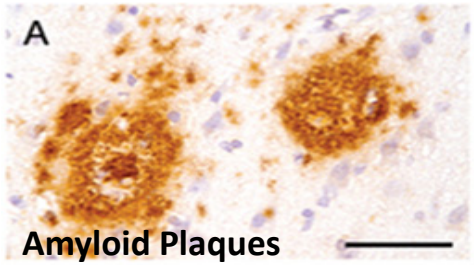
Is it Dementia with Lewy Bodies (DLB) or Lewy Body Dementia (LBD)?

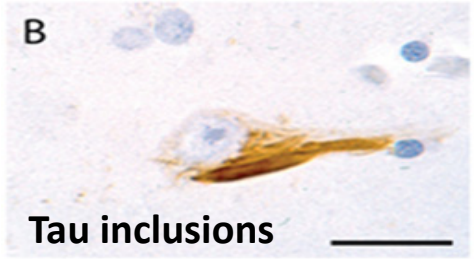
- What are Lewy bodies (LBs)?
- The hallmark brain abnormalities linked to LBD/DLB were discovered by a neurologist called Frederich H. Lewy, MD, (hence the name) who worked with Dr. Alois Alzheimer during the early 1900s
- Aggregated or misfolded alpha-synuclein protein, is the principal component of LBs

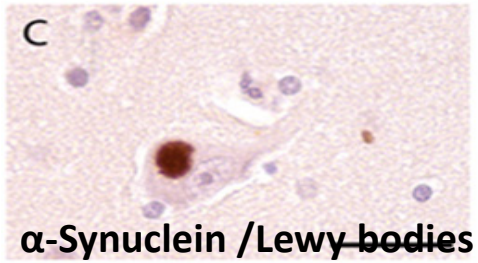


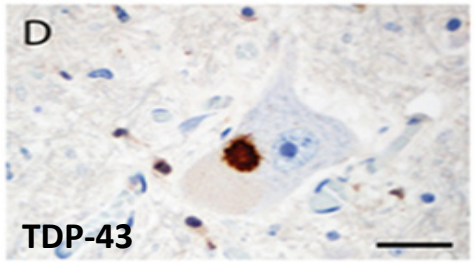
Pathogenic Protein Aggregates in Neurodegenerative Diseases

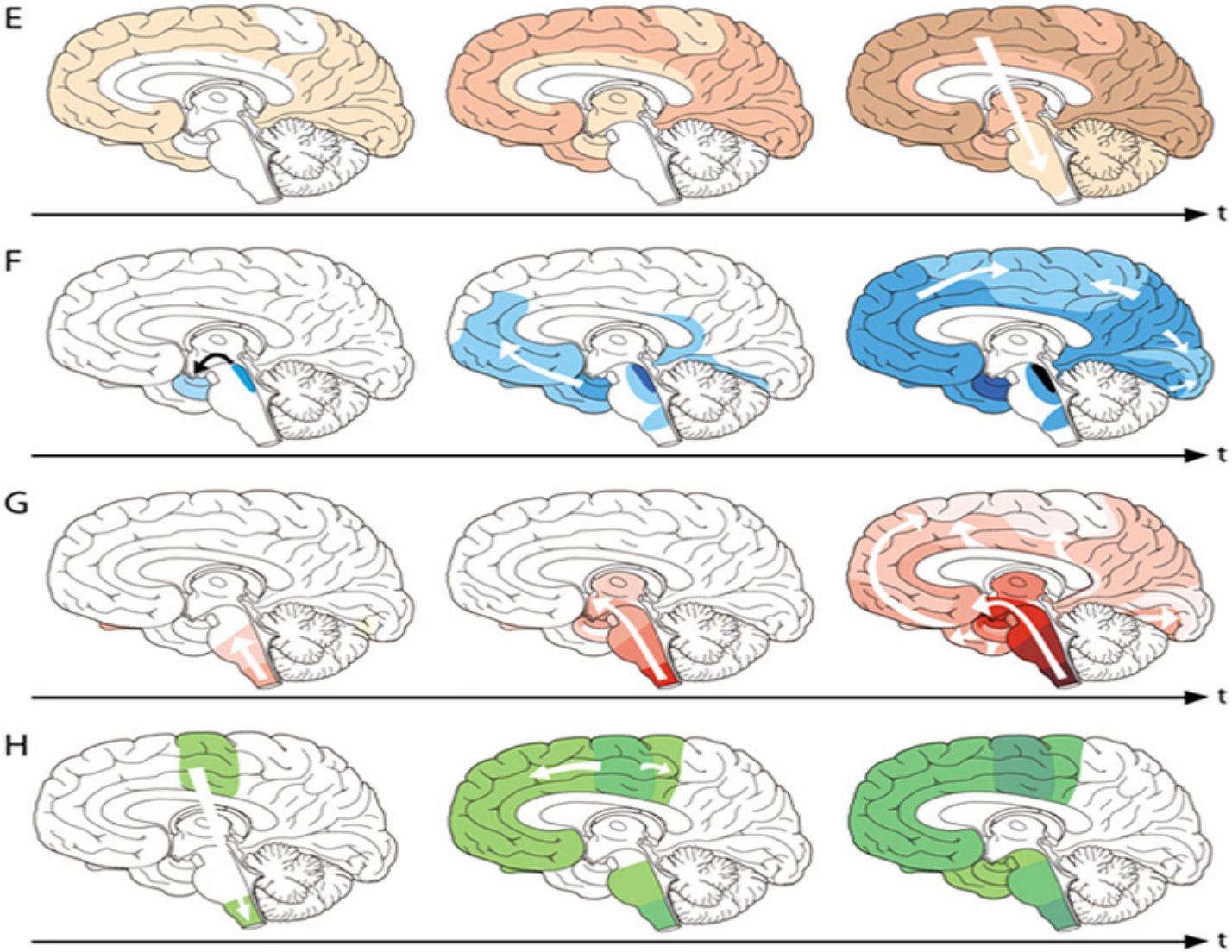
Mathias Jucker & Lary C. 2013 | VOL 501 | NATURE | 45



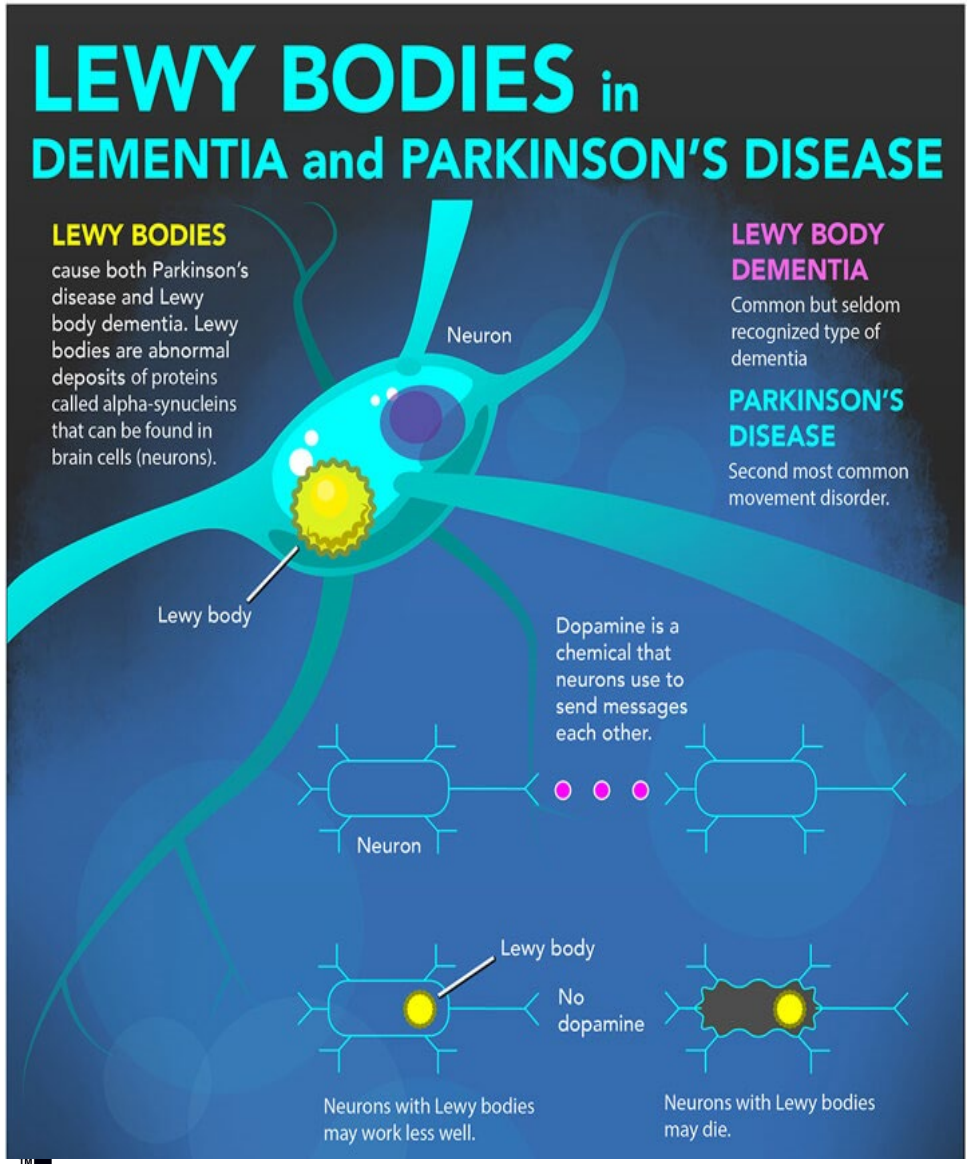


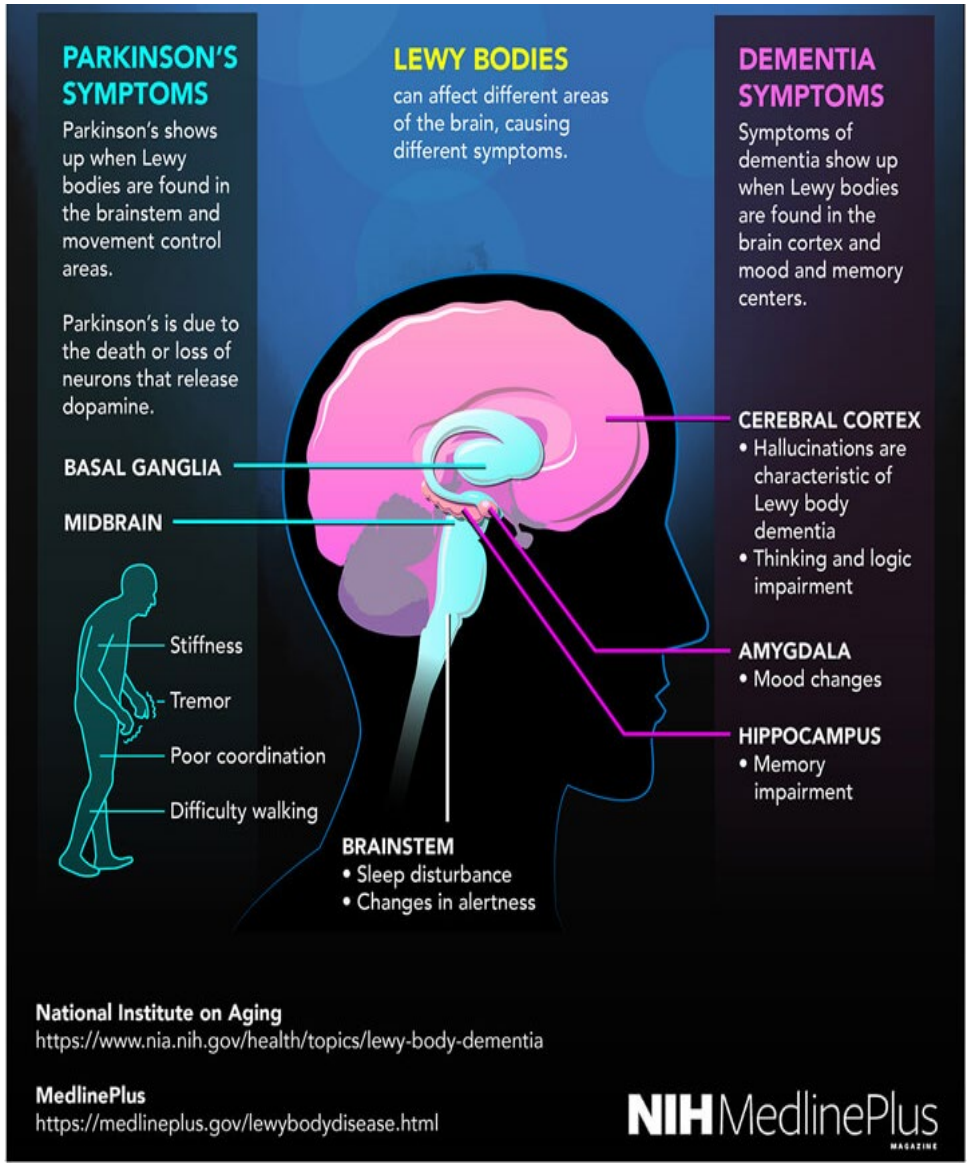






What is Lewy Body Dementia?





Dementia in LBD is Different than Dementia in AD

Has two core features for probable DLB and for possible DLB

- Cognitive fluctuations with pronounced variations in attention and alertness (waxing and waning) and changes in thinking and reasoning
- Confusion and alertness vary significantly from one time of day to another or from one day to the next
- Occurs in 80%-90% of DLB even in early stages of disease compared to 20% of AD, but more frequent in PD as the disease progresses (50%)
- Recurrent visual hallucinations that are well formed and detailed
- Spontaneous parkinsonism (at least one motor feature, including gait, imbalance, and to a lesser extent bradykinesia or rigidity – repeated falls

Other supportive features:

- Neuroleptic sensitivity
- Syncope and transient loss of consciousness
- Systemized delusions
- Trouble interpreting visual information
- Sleep disturbances
- Malfunctions of the autonomic nervous system, eg, hypotension
- Memory loss that may be significant but less prominent than in AD

Dementia with Lewy Bodies/ Lewy Body Dementia

Clinical consensus criteria include two core features (possible LBD/DLB):

- Dementia *
- Parkinsonism – gait/balance disorder, slowness, and frequent falls

Supporting clinical manifestations (at least one)

- Prominent hallucinations and delusions that are sensitive to antipsychotic medication
- Cognitive fluctuations (reduced alertness; waxing and waning)
- Rapid eye movement (REM) sleep disorders (McKeith. Neurology. 1996;47:1113-1124)

* DEMENTIA – DSM-IV

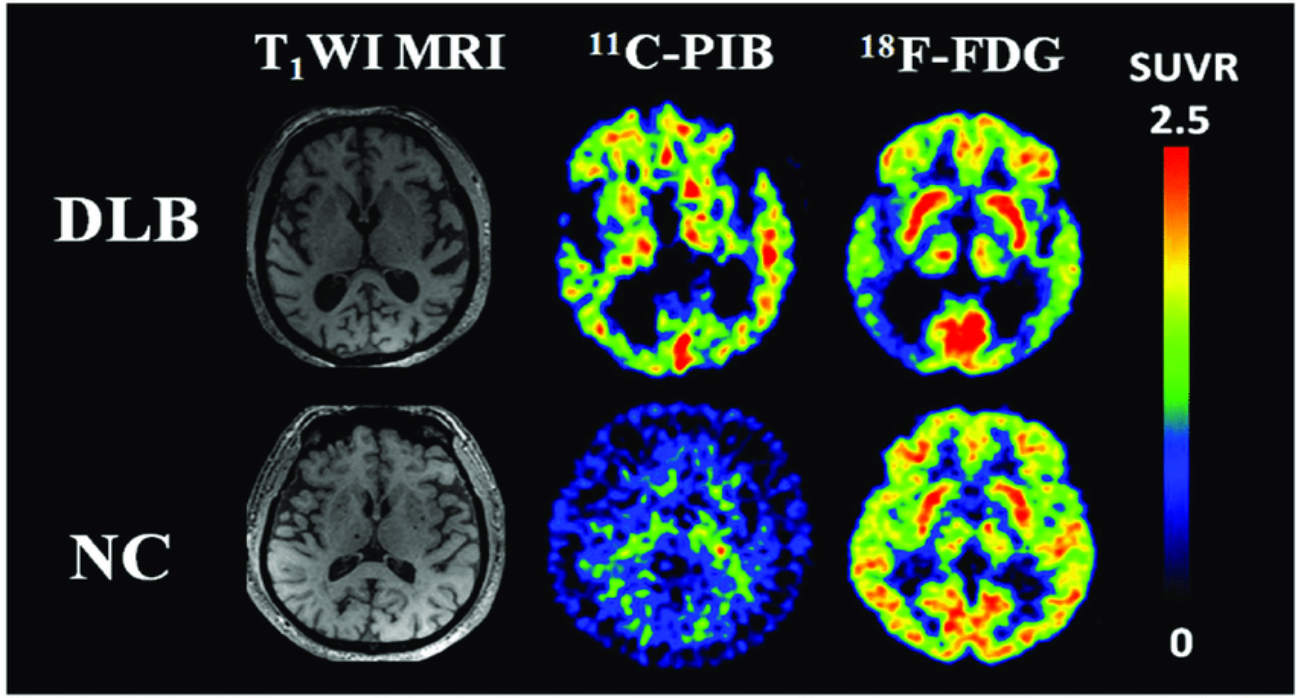
- Prominent or persistent memory impairment in the early stage but occurs with progression
- Attention, frontal-subcortical, and visuospatial

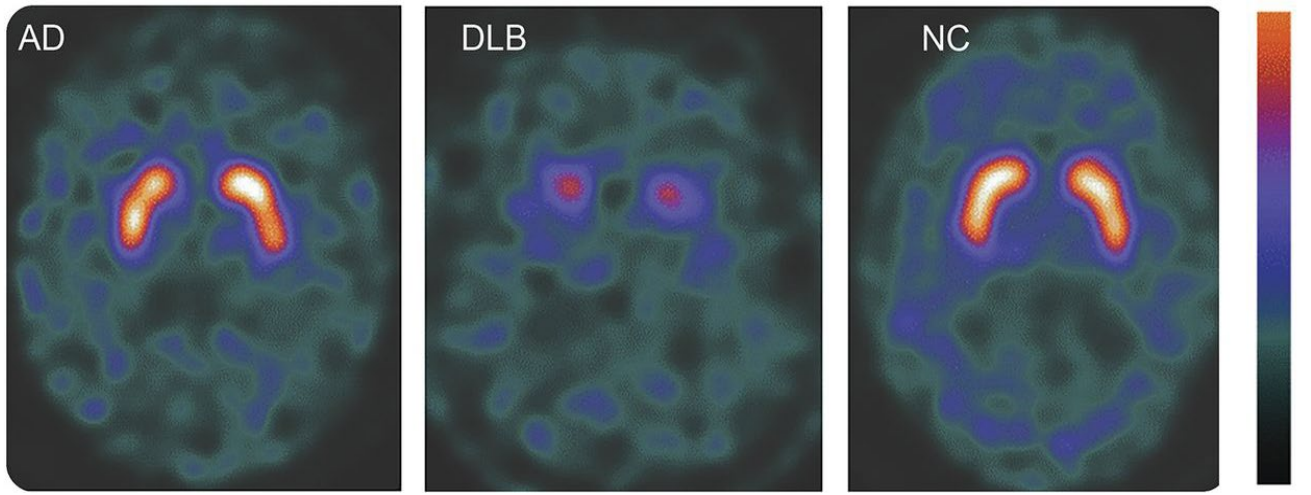
Prevalence

- LBD/DLB is the third most common form of dementia behind Alzheimer's disease (AD) and vascular dementia (VD)
- Represents a pathological mixture of both Parkinson's disease (PD) and AD
- Approximately 1.5 million cases in the US (often misdiagnosed as either PD or AD)
- Accounts to about 30% of all degenerative dementias
- Share motor, cognitive, and behavioral symptoms with PD, AD, and other neurodegenerative diseases

Neuropathology is Shared with AD and PD

- Almost 40%-50% of demented cases show LBs in neocortex and brainstem at autopsies
- Age of onset is comparable to both PD and AD
- Affects more men than women (approx 2:1) and males have more severe decline than females
- Duration is typically rapid and decline is faster than both PD and AD
- Overlapping symptoms suggest that LBD, PD, and Parkinson's disease dementia (PDD) may be linked to same underlying abnormalities in LBs
- Many people with both LB and PDD also have amyloid plaques and tau tangles—hallmark brain changes linked to AD
- LBD patients show brain hypometabolism, more prominently in occipital lobe compared to AD
- LBD typically include PD changes with abnormal DAT scan





Diagnosis

There is no single test that can conclusively diagnose LBD/DLB. The diagnosis is LBD/DLB when:

- Dementia symptoms consistent with LBD develop first
- When both dementia symptoms and movement symptoms are present at the time of diagnosis
- When dementia symptoms appear within one year after movement symptoms or vice versa

Neuropsychology

- Defects of visuo-constructional skills and impaired attention
- Relative sparing of memory

Imaging

- DLB patients have relatively unremarkable MRI of hippocampal volume compared to normal and display less atrophy compared to AD (Hashimoto et al, Neurology 1998)
- Hypo-perfusion is prominent in the occipital lobe compared to both normal and AD patients (Knopman et la, Neurology, 2001)
- Abnormal DaTSCAN comparable to PD
- Widespread Tau (fewer than AD) and plaques pathology similar to AD

Autopsies

- LBs are predominantly in the cortex and brainstem–slightly different than PD where LBs are initially nigrostarial but progress to cortical nuclei
    - Subcortical nuclei, limbic cortex, neocortex (temporal>frontal + parietal)

Clinically Differentiating LBD from PD and AD

- **LBD is conventionally used to describe pathological and clinical features**
- **LBD DIFFERS from AD, PD, and PDD in KEY aspects including:**
  - Early hallucinations: hallucinations, delusions, and misidentification of familiar people are significantly more frequent in early-stage LBD than in AD
  - Cognitive fluctuations (alertness, judgement, and attention) vs memory loss in AD (although memory loss happens later in LBD)
  - Dementia in PDD has distinctive subcortical symptoms and occurs later in disease
  - Dementia in LBD is perhaps the first occurring symptom typically within the first year of patient's complain
  - Dementia and parkinsonism (at least one feature) concurrently occur very early of the disease onset (first year)

Clinically Differentiating LBD from PD and AD (cont'd)

- Autonomic symptoms are concurrent or precede cognitive and motor symptoms: disruption of the autonomic nervous system, causing a blood pressure drop on standing, dizziness, falls, and urinary incontinence, is much more common in early LBD than in AD or PD
- Significantly faster progression and multi-symptomatic than either AD and PD
- Reduced life span (perhaps 50%) compared to AD and PD
- Diagnosis is PDD when a person is originally diagnosed with Parkinson's based on movement symptoms, and dementia symptoms don't appear until a year or more late.
- Since LBs tend to coexist with AD brain changes, it may sometimes be hard to distinguish LB from AD, especially in the early stages.
- REM sleep disorder is more common in early LBD than in AD

Treatment of Lewy Body Dementia

- NO FDA approved medication for LBD
- There are no treatments that can slow or stop neurodegeneration caused by LBD
- Current strategies are symptomatic

<u>Treatment considerations involving medications include:</u>

- Cholinesterase inhibitors
- Antipsychotic drugs: should be used with extreme caution in LBD. Although physicians sometimes prescribe these drugs for behavioral symptoms that can occur in AD, they may cause serious side effects in as many as 50% of those with LBD, such as sudden changes in consciousness, impaired swallowing, acute confusion, episodes of delusions or hallucinations, or appearance or worsening of PD symptoms
- Antidepressants may be used to treat depression, which is common in LBD, PDD, and ADD. The most commonly used antidepressants are selective serotonin reuptake inhibitors (SSRIs)
- Clonazepam may be prescribed to treat REM sleep disorder
- Like other types of dementia and neurodegeneration, LBD is progressive over time and shortens lifespan

Ongoing Clinical Trials in LBD

Agent	Mechanism of action	Sponsor	Phase	Status	Primary outcome measures	Estimated end date
Bosutinib	Tyrosine kinase inhibitor	Georgetown University, Alzheimer's Association	2	Recruiting	Safety and tolerability	Aug 2021
E2027	Selective PDE-9 inhibitor	Eisai	2	Recruiting	MoCA, CIBIC+	July 2025
Pimavanserin	Selective 5-HT2A inverse agonist	Acadia, NIA	3	Completed	Time to relapse	Completed
LY3154207	Dopamine D1 receptor modulator	Eli Lilly	2	Completed	Continuity of Attention score of CDR-CCB	Sept 2020
K0706	Tyrosine kinase inhibitor	Georgetown University, Sun Pharma	2	Recruiting	Safety and tolerability	Aug 2022
Nilotinib	Tyrosine kinase inhibitor	Georgetown University, NIH	2	Recruiting	Safety and tolerability	March 2023
Neflamapimod (VX-745)	P38 MAP kinase alpha inhibitor	EIP Pharma	2	Completed	NTB	Jun 2020
MP-101	mGluRs 2/3 agonist	Mediti Pharma	2	Completed	NPI – psychosis subscale	Aug 2020

Case Study 1

A 62 year old man presented to the memory clinic with sudden onset confusion. His wife asserts that he is an accountant and used to pay very much attention to details. He was extremely neat and organized. He is healthy with no prior diagnosis of any disease and never took any medications other then regular OTCs occasionally. His wife noticed increased clumsiness, with more confusion as the day progresses. He often got lost driving a very familiar 3 miles road to their married daughter. His sleep has become more problematic in the last 6-8 months. He often complains that he will fall if he does not lean over something. His brain MRI was unremarkable, and blood workup revealed no abnormalities. No family history of neurodegenerative diseases. His MMSE was 21 on visit 1 (December 15, 2018) but 3 months later (March 1, 2019) his MMSE improved to 30, without any treatment. His neurologist recommended a monoamine oxidase inhibitor and donepezil. Three months later his motor symptoms slightly improved but continued to show cognitive fluctuations, sleep disturbances and acting out his dreams. The likely diagnosis is:

A. Alzheimer's disease
B. Parkinson's disease
C. Depression
D. Huntington's disease
E. Dementia with Lewy bodies

Case Study 2

A 74 year old woman with family history of Alzheimer's disease was diagnosed with Parkinson's disease 6 years ago. The patient was receiving 600 mg daily levodopa and an antidepressant. Prior DatSCAN revealed some abnormalities that did not worsen 4 years later. Her memory declined significantly in the last 12 months and her MoCA is 24/30. She responded better to acetylcholinesterase inhibitors (memantine) but she still showed slight decline. She is getting more psychosis and delusion. She did well on pimanvanserin with complete absence of psychosis.

This patient is likely to be diagnosed with:

A. Lewy body dementia
B. Parkinson's progression to Alzheimer's disease
C. Vascular dementia
D. Parkinson's' disease dementia

Case Study 3

A 55 year old male, with no history of depression or dementia complained of constantly feeling down, exhibited 1-2 events of suicidal ideation, his memory is great but he tends to be very irritable, agitated, with a clear mind in the morning hours and a “foggy brain” and less interested in his surroundings at other times of the day. The patient did fall a few times over the last year. He has visual hallucinations and his wife says that he often tells her “out of the blue” about the little harmless soldiers in his garden. His MoCA is 28/30 twice in the row and 3 months apart. His MRI was unremarkable but 18F-PDG revealed hypometabolism throughout his brain and mainly in his occipital lobe. Levodopa challenge showed little symptomatic effect. His physician aims to confirm diagnosis using available imaging techniques in the hospital, to determine the probable cause of his behavioral and cognitive symptoms. She recommends:

A. Amyloid positron emission tomography
B. CT scan to look for minor infarcts
C. A volumetric MRI of the hippocampus
D. DAT SCAN
E. Lumbar puncture to measure tau, amyloid and alpha-synuclein
F. All of the above

References

1. Jellinger KA, Korczyn AD. Are dementia with lewy bodies and parkinson's disease dementia the same disease? *BMC Med*. 2018;16(1):34. Accessed Apr 30, 2021. doi: 10.1186/s12916-018-1016-8.

2. Galasko D. Lewy body disorders. *Neurol Clin*. 2017;35(2):325-338. Accessed Apr 30, 2021. doi: 10.1016/j.ncl.2017.01.004.

3. Tampi RR, Young JJ, Tampi D. Behavioral symptomatology and psychopharmacology of lewy body dementia. *Handb Clin Neurol*. 2019;165:59-70. Accessed Apr 30, 2021. doi: 10.1016/B978-0-444-64012-3.00005-8.

4. Tampi RR, Young JJ, Tampi D. Behavioral symptomatology and psychopharmacology of lewy body dementia. *Handb Clin Neurol*. 2019;165:59-70. Accessed Apr 30, 2021. doi: 10.1016/B978-0-444-64012-3.00005-8.

5. Gomperts SN. Lewy body dementias: Dementia with lewy bodies and parkinson disease dementia. *Continuum (Minneap Minn)*. 2016;22(2 Dementia):435-463. Accessed Apr 30, 2021. doi: 10.1212/CON.0000000000000309.

6. Stinton C, McKeith I, Taylor J, et al. Pharmacological management of lewy body dementia: A systematic review and meta-analysis. *Am J Psychiatry*. 2015;172(8):731-742. Accessed Apr 30, 2021. doi: 10.1176/appi.ajp.2015.14121582.

7. Sezgin M, Bilgic B, Tinaz S, Emre M. Parkinson's disease dementia and lewy body disease. *Semin Neurol*. 2019;39(2):274-282. Accessed Apr 30, 2021. doi: 10.1055/s-0039-1678579.

8. Chin KS, Teodorczuk A, Watson R. Dementia with lewy bodies: Challenges in the diagnosis and management. *Aust N Z J Psychiatry*. 2019;53(4):291-303. Accessed Apr 30, 2021. doi: 10.1177/0004867419835029.

References

9. Outeiro TF, Koss DJ, Erskine D, et al. Dementia with lewy bodies: An update and outlook. *Mol Neurodegener*. 2019;14(1):5. Accessed Apr 30, 2021. doi: 10.1186/s13024-019-0306-8.

10. Jellinger KA. Dementia with lewy bodies and parkinson's disease-dementia: Current concepts and controversies. *J Neural Transm (Vienna)*. 2018;125(4):615-650. Accessed Apr 30, 2021. doi: 10.1007/s00702-017-1821-9.

11. Outeiro TF, Koss DJ, Erskine D, et al. Dementia with lewy bodies: An update and outlook. *Mol Neurodegener*. 2019;14(1):5. Accessed Apr 30, 2021. doi: 10.1186/s13024-019-0306-8.

12. Hershey LA, Coleman-Jackson R. Pharmacological management of dementia with lewy bodies. *Drugs Aging*. 2019;36(4):309-319. Accessed Apr 30, 2021. doi: 10.1007/s40266-018-00636-7.

13. Taylor J, McKeith IG, Burn DJ, et al. New evidence on the management of lewy body dementia. *Lancet Neurol*. 2020;19(2):157-169. Accessed Apr 30, 2021. doi: 10.1016/S1474-4422(19)30153-X.

14. Kenny ER, Blamire AM, Firbank MJ, O'Brien JT. Functional connectivity in cortical regions in dementia with lewy bodies and alzheimer's disease. *Brain*. 2012;135(Pt 2):569-581. Accessed Apr 30, 2021. doi: 10.1093/brain/awr327.

15. Schumacher J, Peraza LR, Firbank M, et al. Dysfunctional brain dynamics and their origin in lewy body dementia. *Brain*. 2019;142(6):1767-1782. Accessed Apr 30, 2021. doi: 10.1093/brain/awz069.

16. Sanford AM. Lewy body dementia. *Clin Geriatr Med*. 2018;34(4):603-615. Accessed Apr 30, 2021. doi: 10.1016/j.cger.2018.06.007.

Thank You