Dementia with Lewy Bodies

An overview for the community

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No conflicts of interest to declare

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Goals

Terminology	Etiology	Clinical criteria	Management	Apply
Be able to use terminology correctly	Discuss pathophysiology	Be aware of current clinical criteria and diagnostic tools	Know management criteria	Apply concepts to a real-life case

Synucleinopathies: Facts and terminology

***Panel 1:* Dementia terminology**

Lewy body dementias
An umbrella term that includes clinically diagnosed dementia with Lewy bodies and Parkinson's disease dementia.

Dementia with Lewy bodies
Dementia that occurs before or concurrently with parkinsonism or within 1 year of onset of motor symptoms. However, not all patients develop parkinsonism.[2]

Parkinson's disease dementia
Dementia starting 1 year or more after well established Parkinson's disease.[1]

Mild cognitive impairment in Parkinson's disease
Cognitive impairment in patients with Parkinson's disease not sufficient to interfere greatly with functional independence.[3]

Lewy body disease
Pathological diagnosis. The distribution of Lewy body-type pathology and additional pathologies is often specified.

Major and mild neurocognitive disorder with Lewy bodies or due to Parkinson's disease
New terms proposed by DSM-5[4] corresponding to dementia with Lewy bodies and Parkinson's disease dementia.

DSM-5=Diagnostic and Statistical Manual of Mental Disorders, fifth edition.

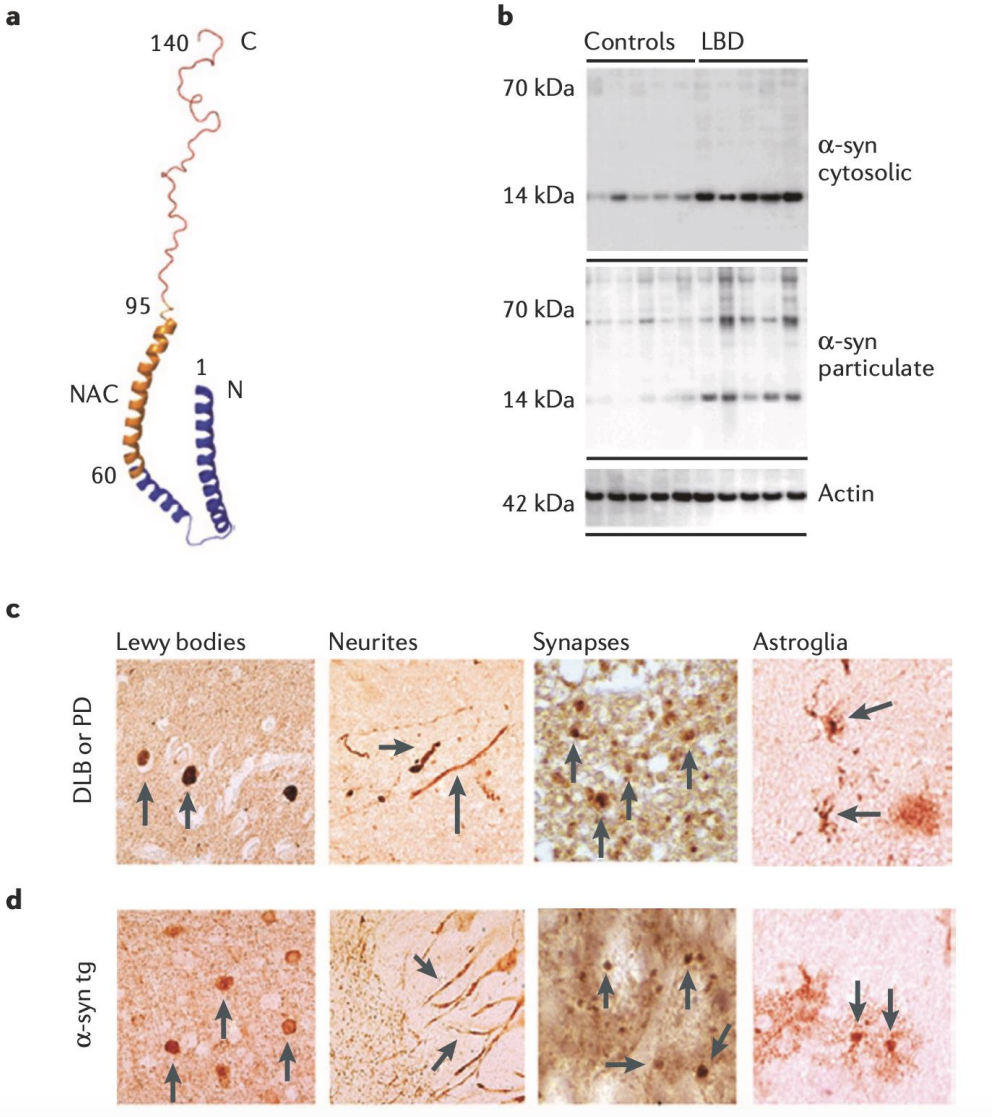
Multiple systems atrophy (MSA): predominant parkinsonism and dysautonomia with cerebellar and/or spinal cord pathology. Usually no dementia. Glial pathology

- A group of neurodegenerative disorders
- Alpha-synuclein (a-syn) aggregation in nervous system
- The 2nd disease to cause dementia after AD
- Age 70-85, many are early-onset
- Often co-occurring with AD
- More common in men

Lancet 2015; 386: 1683–97

Pathophysiology

- Alpha-synuclein is encoded by SCNA gene on chr 4q21
  - 140 aa soluble protein monomer
  - With lipid membrane, prone to fold into dimers and oligomers
  - Aggregates usually 1% of normal protein in cytosol.
- Expressed in hippocampus, thalamus, cerebellum, glia.
- Spliced variants 126 AA, lacks exon 3, 122-AA lacks exon 5.
- Aggregates are phosphorylated, nitrated and truncated
- Aggregates cause neuron toxicity and loss:
  - Loss of acetylcholine: reduced memory and learning
  - Loss of dopamine: behavior, movement, mood, cognition
  - Other neurotransmitters altered.
- **PD**: Lewy bodies are mostly *subcortical* at first, then widespread
- **DLB**: Lewy bodies are mostly *cortical* and *widespread* from the onset
- **MSA**: Lewy bodies are mostly in *glial cells*



Nat Rev Neurosci. 2013 Jan;14(1):38-48.

Clinical features of Lewy Body Dementias

Presence of dementia: Cognitive decline affecting one or more IADLS/ADLs

A prodromal stage exists, called MCI-LB, when patients have core features, but not dementia.

Determine the first symptom and timeline: Can be difficult after onset. One year rule

1. PDD presents in the setting of established PD (duration of at least 1 y)
2. DLB presents when cognitive changes precede or occur together with the onset of parkinsonism.

DLB Core clinical features:

Dream enactment behavior
Fluctuations
Well-formed visual Hallucinations
Parkinsonism

DLB Supportive clinical features:

Antipsychotics sensitivity
Autonomic dysfunction
Minor hallucinations and misperceptions
- Passage phenomenon
- Extracampine hallucinations

Delusions
Depression and anxiety
Hypersomnia
Hyposmia

The Lancet Neurology 19, no. 2 (February 1, 2020): 157–69.

Fluctuations

- Spontaneous changes in levels of alertness. Can resemble delirium.
- Present in 90% of DLB patients
- Can be difficult to elicit:
  - Staring in to space / Blank stare / looking "lost"
  - Suddenly unable to finish thoughts
  - Drowsiness/Sleepiness
- **Mayo fluctuations score:** Score pf 3-4 more often in DLB, 1-2 more often in AD

Are there times when the patient's flow of ideas seem disorganized, unclear or not logical?

How often is the patient drowsy and lethargic during the day, despite getting enough sleep the night before?

- All the time or several times a day
- Once a day or less

How much time does the patient spend sleeping during the day (before 7:00pm)?

- 2 hours or more
- Less than 2 hours

Does the patient stare into space for long periods of time?

Ferman et al. Neurology 2004;62;181-187

Well formed visual hallucinations

- Occur in 80% of patients with DLB, distinctive if ***early***
- Often preceded by minor hallucinations or visual illusions
- To be a core criterion they must be ***well formed / detailed***
- Can be threatening or non-threatening.
- Can have sudden onset. Need to be ***repetitive***.
- More common in **women** and in DLB compared to PDD
- Can occur in PDD in response to levodopa or dopamine agonists.

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Parkinsonism

- Defined as bradykinesia + rigidity, which are present in 80% of DLB
- Resting tremor is less common in DLB compared to PD
- Causes increased disability
- Responsive to to levodopa: less reponse in DLB compared to PD.
- Swallowing can become affected
- Speech is hypophonic, can affect communication.
- Tendency to retropulsion on pull test is a risk for falls.

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REM Sleep behavior disorder

- Present in 76% of patients with DLB
- Absence of REM sleep physiologic atonia:
  - Movements and acting out of dreams: punching/kicking, complex movement
  - Can cause falls from bed, injuries to patient and bed partner
  - Usually *later part of night*, when REM sleep is more abundant
  - Patients can sometimes remember dream but not always
  - Does NOT include physiologic twitches, hypnagogic or hypnopompic events
- Onset can be decades prior to full syndrome.
  - 75-90% Primary RBD develops LBD
- Can be secondary to other factors
  - Note that you **cannot** count secondary RBD for criteria
  - E.g., secondary to SSRI, OSA, sleep apnea, pontine strokes

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Supportive criteria: less specific.

Sensitivity to antidopaminergics: can be irreversible, *please do not attempt as diagnostic tool*

- AVOID HALOPERIDOL and all strong D2 antagonists (Risperidone, Reglan, etc.)
- Increased risk of mortality, neuroleptic malignant syndrome.

Autonomic dysfunction: 90% prevalence in DLB

- Orthostatic hypotension
- Constipation
- Urinary frequency
- Cold/Heat intolerance
- Cardiac arrhythmia and bradycardia (some DLB patients have PM years before onset of symptoms)
- Syncope

Minor hallucinations and misperceptions:

- extracampine phenomenon
- auditory hallucinations are less likely

Systematized delusions, usually later in the course:

- Paranoia of burglary, infidelity
- Capgras phenomenon or impostor syndrome: detachment of emotion from face

Depression, anxiety, apathy

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Testing/Biomarkers

In clinic look for these:

- Cognitive exam: visuospatial/executive and attentive deficits, relatively spared memory
- Motor features: masked facies, hypophonia, bradykinesia, rigidity, tremor, camptocormia, shuffling gait.
- Measure orthostatic vital signs

Table 1
Imaging in Lewy Body Dementia (LBD).

Imaging Modality	Findings in LBD	Comments
Indicative Criteria		
SPECT/PET	Decreased dopamine transporter uptake in basal ganglia	Differentiates between AD and LBD
^{123}I-MIBG scintigraphy	Decreased uptake in myocardium	Specific for LBD. Differentiates between AD and LBD
Polysomnography	REM sleep without atonia	Highly specific for LBD
Supportive Criteria		
CT/MRI	No to minimal medial temporal lobe atrophy	Most consistent finding. Differentiates between AD, PDD, and LBD
FDG-PET	Hypometabolism in medial temporal lobes	Differentiates between AD and LBD
	Cingulate island sign	
EEG	Prominent posterior slow-wave activity with periodic fluctuations in the pre-alpha/theta range	Highly sensitive and specific.

New biomarkers (Out of pocket):
CSF Alpha synuclein aggregation assay: (SAA-Amplify): up to 89% accurate.

Skin biopsies: location of biopsy matters. Experienced pathologist

Prasad, Sakshi. "Recent Advances in Lewy Body Dementia: A Comprehensive Review," 2023.

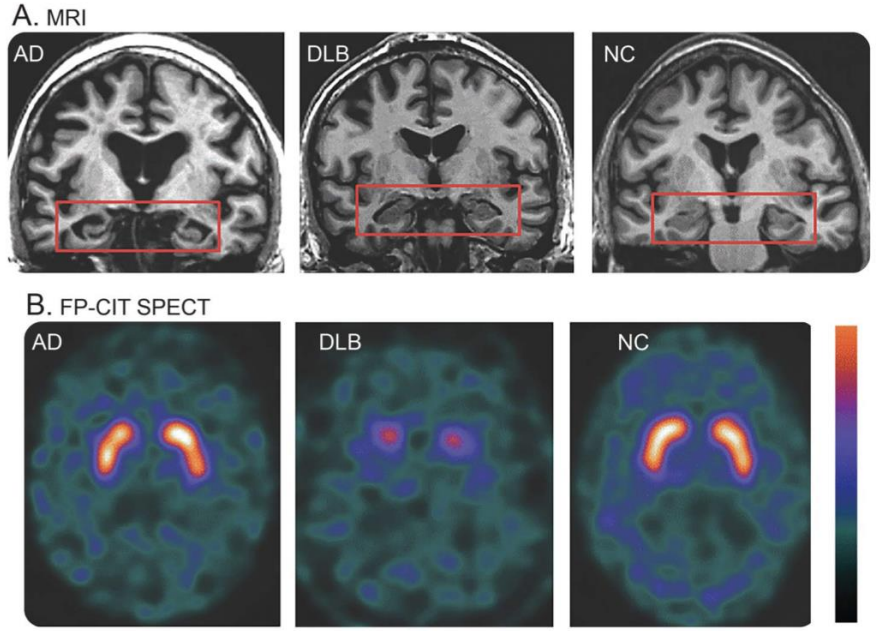


Figure 3 Polysomnographic (PSG) recordings

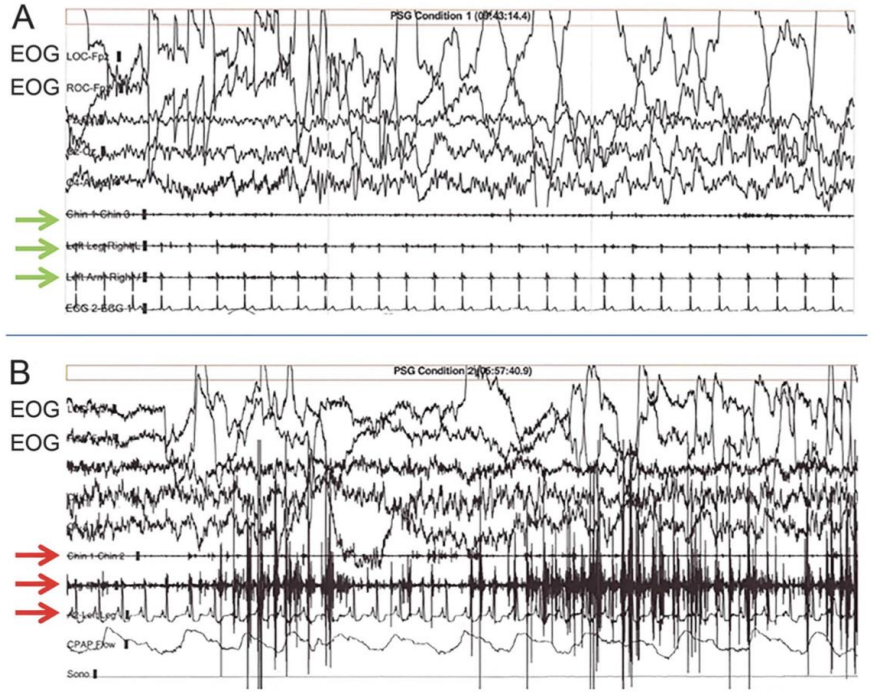
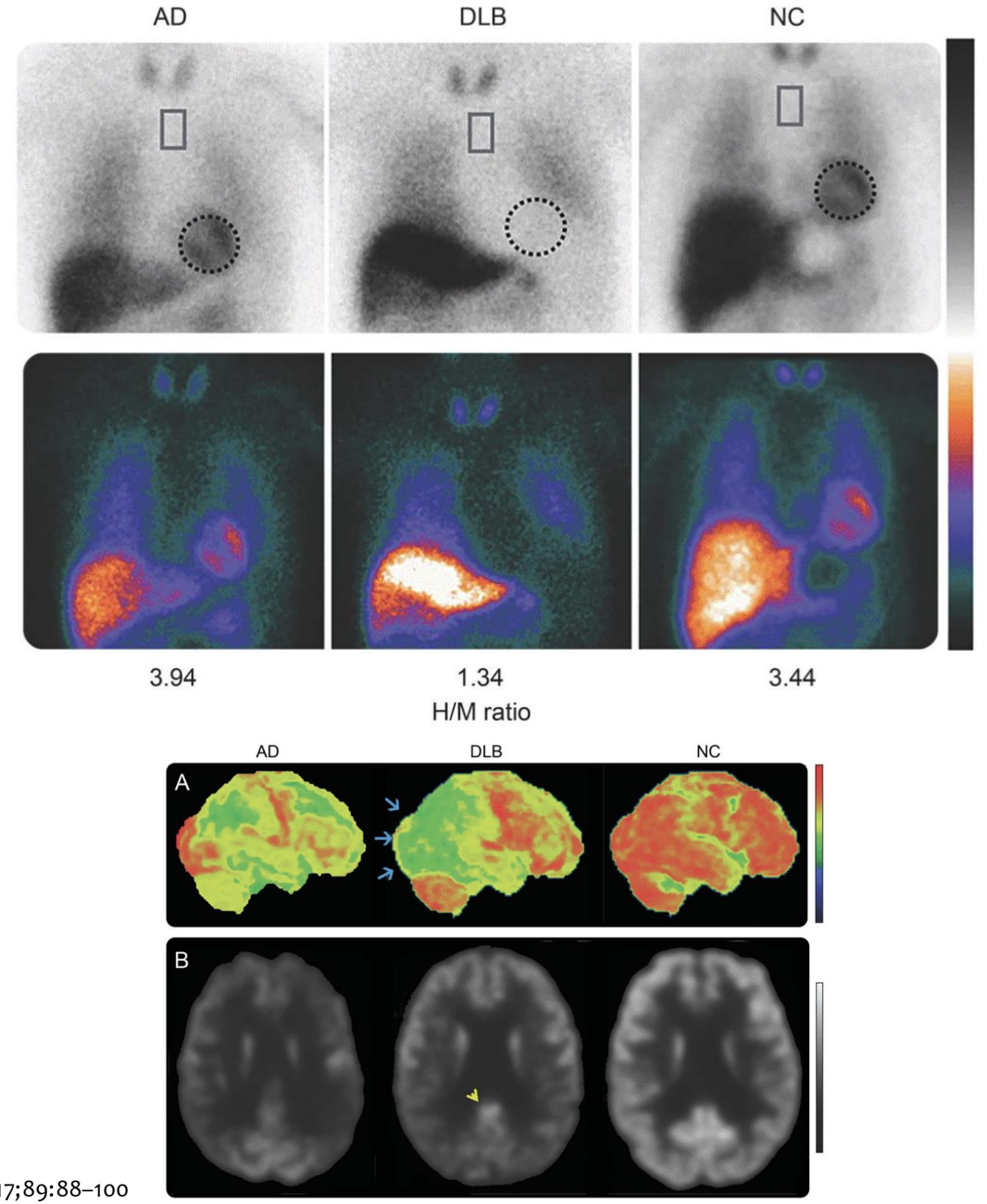


Figure 2 ^{123}Iodine-metaiodobenzylguanidine myocardial imaging in patients with Alzheimer disease (AD), dementia with Lewy bodies (DLB), and age-matched normal controls (NC)



McKeith et al. Neurology 2017;89:88–100

Revised criteria for the diagnosis of DLB

Probable DLB:

- Must have dementia
- Two or more core clinical features (first 3 are *early*)
  - Fluctuations
  - Well formed hallucinations
  - Acting out of dreams
  - Parkinsonism (within a year of or after onset of dementia)
- One core clinical feature with 1+ indicative biomarkers.
  - DAT scan positive
  - MIBG scintigraphy
  - REM sleep atonia on polysomnogram

Possible DLB

- Must have dementia
- One core biomarker alone without supportive biomarkers
- One or more indicative biomarkers but no core features.

DLB *less* likely if

- Other reason for symptoms
  - Diffuse vascular disease
  - Physical illness
  - Different brain disorder.
- Parkinsonism is only core clinical feature starting in late stages of dementia

McKeith et al. Neurology 2017;89:88–100

Management

No FDA-approved treatments, mostly supportive

Nonpharmacologic interventions:

- Exercise has both motor and cognitive benefits.
- Cognitive training
- Structured activities to maintain engagement
- Caregiver-oriented education and training to manage psychiatric symptoms
- Cognitive Behavioral Therapy in early stages

Pharmacologic management:

- Cognitive symptoms
- Neuropsychiatric symptoms
- Motor symptoms
- Sleep and autonomic symptoms

Cognitive and neuropsychiatric symptoms

pharmacological treatments

Cholinesterase inhibitors: rivastigmine and donepezil

- Improve cognitive+ global function and activities of daily living
- Even if no improvement, protect against faster decline (while pt is on them)
- Can reduce visual hallucinations and improve fluctuations, sometimes needs higher doses compared to AD.
- *Note: we only treat threatening hallucinations*

Memantine:

- less clear efficacy, but may have benefits
- usually well tolerated as single therapy or with cholinesterase inhibitors

AVOID ANTIPSYCHOTICS AS MUCH AS POSSIBLE!!

- **No injectables, no haloperidol, no first-line antipsychotics (including Reglan!)**
- Limited evidence for quetiapine as a safer option. Possibly clozapine (but more side effects, requires frequent CBC)
- Pimavanserin (waiting on clinical trials specific for LBD)

SSRIs, buspirone, trazodone and mirtazapine

- can help anxiety and depressive symptoms
- can help with agitation in some cases
- **Some DLB patients can be hypersensitive to all psychoactive drugs:** make small, slow and single changes

McKeith et al. Neurology 2017;89:88–100

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Motor symptoms

Aggressive neuro PT/OT throughout the year as possible

Regular exercise and stretching

LOUD Speech Therapy for hypophonia

Swallow testing if suspecting dysphagia

Ca/Vit D supplementation. Screen for osteoporosis

Can try Sinemet (Carbidopa-Levodopa)

- Start with very low doses (e.g. 25/100 mg, ½ tab TID)
- Slow up titration (e.g., increase by ½ tab every week)
- Increase only to lowest effective dose
- Risk is inducing psychosis and autonomic dysfunction – counsel patient. Stop if hallucinations

Deep brain stimulation contraindicated due to dementia

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Dream enactment behavior

First line is melatonin. Can find OTC.

- Start with 3 mg.
- Dose to address REM behavior disorder may need to be as high as 20 mg

Sometimes SSRIs can trigger secondary RBD –

- Avoid nighttime dosing of SSRI as possible if RBD is severe.

Second line: benzodiazepines (e.g. clonazepam)

- Limit use to only severe RBD

Padded bed railings

Remove obstacles around bed as possible

Have partner sleep in separate room

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Autonomic symptoms

Constipation:

- Regular miralax, fiber
- Goal is 1 BM every other day or more frequent
- Cholinesterase inhibitors may help with this goal
- May need GI referral

Orthostatic hypotension (and supine hypertension)

- Hydration
- Gradual position change
- Compression stockings 20-30 mmHg when out of bed (may need thigh-high)
- Midodrine during daytime, enalapril at night
- Avoid calcium channel blockers

Skin may get dry, susceptible to Seborrhoic Keratitis

Urinary frequency

- Scheduled bathroom breaks, limit water before bed
- Avoid anticholinergics like trospium, oxybutynin, solifenacin, tolterodine, etc
- Prefer mirabegron or vibegron (can be expensive)
- Urology referral to rule out comorbidities, consider botox injections

Higher risk of arrhythmia

McKeith et al. Neurology 2017;89:88–100

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Case presentation: 71 yo right-handed F

Symptom onset around late 2022 – difficulties with **directions while driving**, leading to family asking her to stop drive due to concern.

Around January 2023 – more **memory** changes, difficulties remembering conversations, events, dates, worse since spring/summer. Around that time, more trouble with **multitasking/concentration**, evidenced by inability to finish projects/tasks, getting overwhelmed/confused.

Significant **anxiety**, more in the summer 2023, around this time, more **hallucinations** – people/strangers in the house – concerned about women in the backyard, which are strangers to her.

Bsome days and less other days but no clear fluctuations otherwise

In 2023-2025, admitted to memory care facility after her husband died, and could not remember this, wishing to call/see her husband. Thinks she is working at the memory care facility. More agitation/anxiety.

Other areas

Motor: Able to play with her grandkid in 2023, had one fall chasing him, otherwise no falls. In 2025 occasional postural BUE tremors and slower gait. Initially no handwriting difficulties. No significant dysphagia, no dysarthria.

Significant insomnia. Occasional daytime somnolence. **Report significant acting out of dreams for years.** Punches and kicks.

Functional status: more help needed with medications since spring 2023, cannot cook safely due to multiple times leaving stove on. Needs help with appointments and finances.

ADLS intact upon presentation

By 2025 requiring more assistance for showering/hygiene reminders, eating.

Social history

- Admitted to memory care after husband suddenly passed away
- Completed one year of college, no learning disabilities.
- Worked in child-care and clerical work, retired in her early 60s, unrelated to any cognitive or psychiatric issues.
- No alcohol use, former tobacco smoker, no recreational drugs

Family history

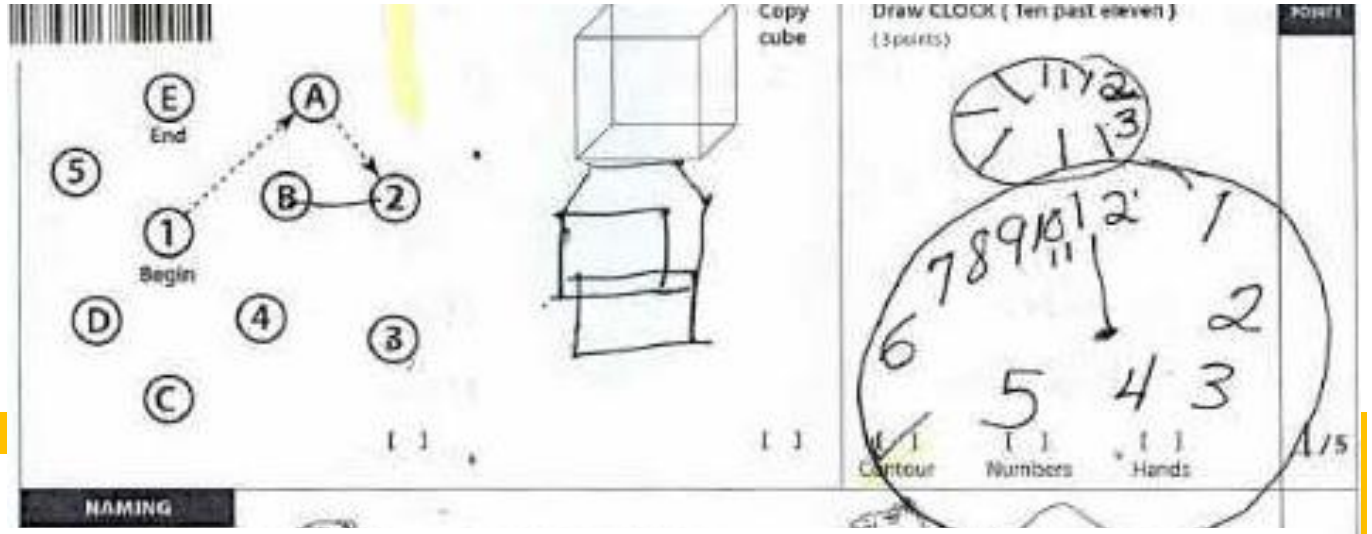
- Unknown, patient adopted

PMH and surgeries

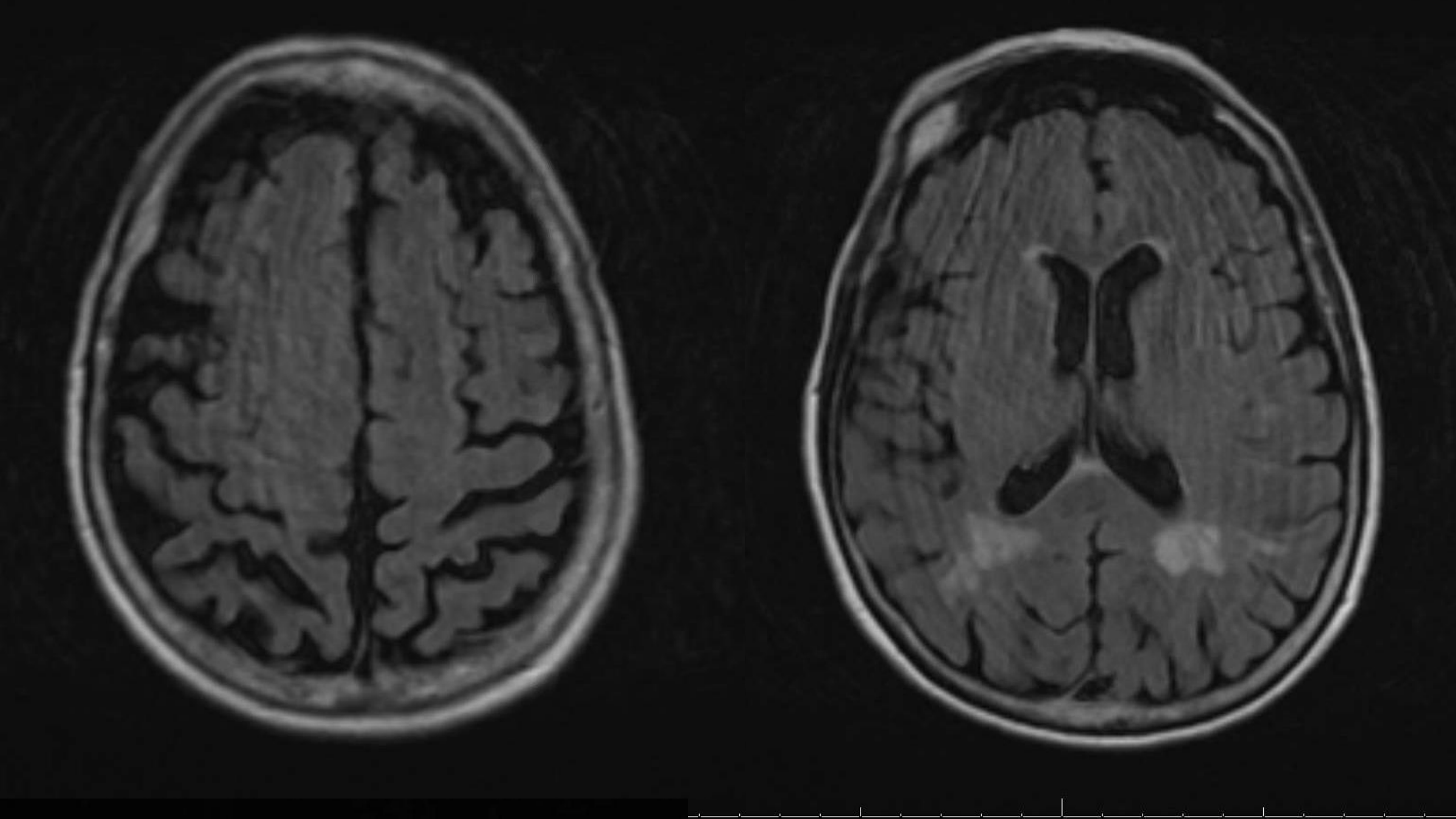
- Hyperlipidemia
- Hearing loss
- Prior appendectomy
- Prior minor R eye surgery
- Frequent UTIs

Wears glasses and hearing aids.

Exam:



- General: thin, anxious, frustrated at family for reporting history, anosognosia, tearful
- Pressured speech, distractable, answers tangentially to questions
- MOCA 9/30 upon presentation in 2023 - points missed: trails, figure copy, clock numbers, clock hands, naming (- 1, got with cue), calculations (- 3), repetition (- 2), fluency, abstraction (- 1), memory (- 5; note registration **2/0/1** on consecutive trials, cued recall **+ 1 with category cues, + 3 with multiple choice cues**, 5 false positives), and orientation (- 4)
  - Phonemic fluency 8 F words, 0 repeats
  - Semantic fluency 7 animals, 1 repeat.
  - ‘World’ back 2/5
- Neurological at presentation: no rigidity, only paratonia, no parkinsonism otherwise, antalgic gait due to knee injury. Saccades full.
- By 2025: unable to come to clinic due to anxiety/exit seeking, visible occasional postural BUE tremors, more stooped, more repetitive/anxious



Lumbar puncture

- Opening pressure: normal
- Cell counts within limits, mildly hematic, normal protein/glucose, no oligoclonal bands, negative autoimmune encephalopathy markers (serum and CSF)

- Mayo ADEVL:
  - ATI **0.131** (≤ 0.028), Abeta42 913 (>834),
  - Total Tau **1270** (≤238), Phospho-tau 181: **120** (≤21.6)
- RT QUIC negative, high 14-3-3 and TAU (was done due to very high tau)
- SynTAP POSITIVE.

Discussion

- Meets clinical criteria for probable DLB:
  - Dream enactment behavior
  - Well formed hallucinations
  - Possible fluctuations, harder to define with family
  - More recently some tremors of BUE, appear postural, no parkinsonism yet.
- Rapid progression of symptoms in 12-14 months, leading to institutionalization, difficulties with controlling behavioral changes.
- Numerous recent UTIs. Looking into urology referral.
- Presence of AD co-pathology, but not enough to justify all the symptoms, utility of Syntap in this case.

Future planning/Points of discussion

Plan to optimize dosing of trazodone and buspirone before decision to stop.
Ongoing education of facility personnel as to nonpharmacological strategies
Mirtazapine instead of trazodone.
Increase quetiapine.
Last choice – consider Pimavanserin - but insurance may not approve.
Clozapine complicated to do in memory care - risk of agranulocytosis
Additional options? – wishing to avoid antipsychotics other than quetiapine.