Shaking Things Up:

Recognizing and Managing Parkinson's Plus Syndromes

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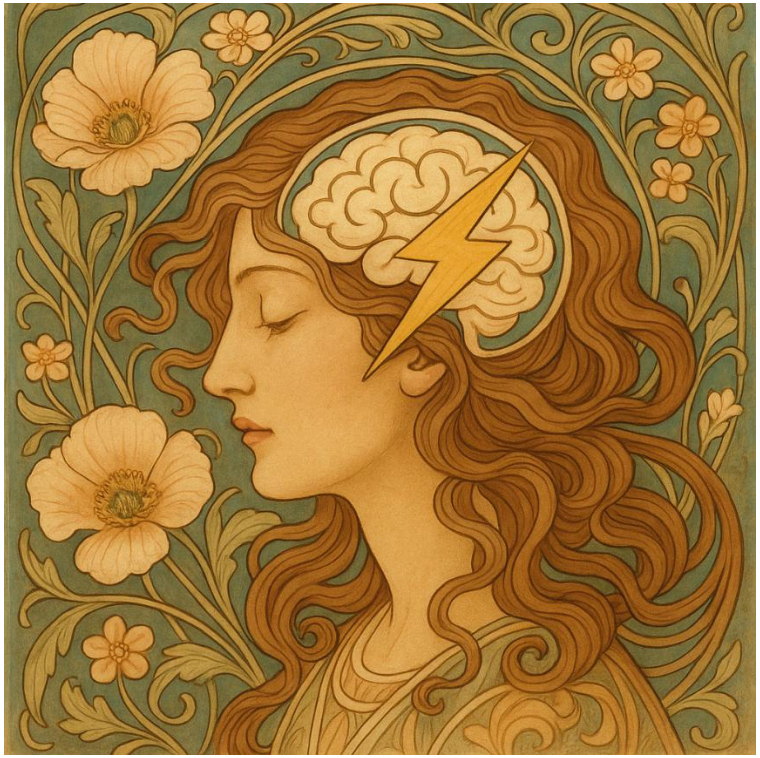
Outline + Objectives

- Case
- Introduction to parkinsonism
- Parkinson’s Plus Sx
- Management considerations
- Summary



Why this matters

- More than 110,000 Canadians > 40 live with parkinsonism
  - 10-15% are Parkinson's Plus syndromes
- Often misdiagnosed as iPD
  - Different natural histories/progression
    - Confusing & distressing for patients and caregivers
  - Risk of ineffective/harmful medications
  - More accurate diagnosis helps guide supports and interdisciplinary management

(Hirschbichler et al. 2017)

Case

78M, frequent falls, apathy, visual hallucinations, Capgras, forgetful, can't use the TV remote, moving "slow" + gets "stuck" walking, hard to get out of a chair or turn over in bed, severity of symptoms fluctuate

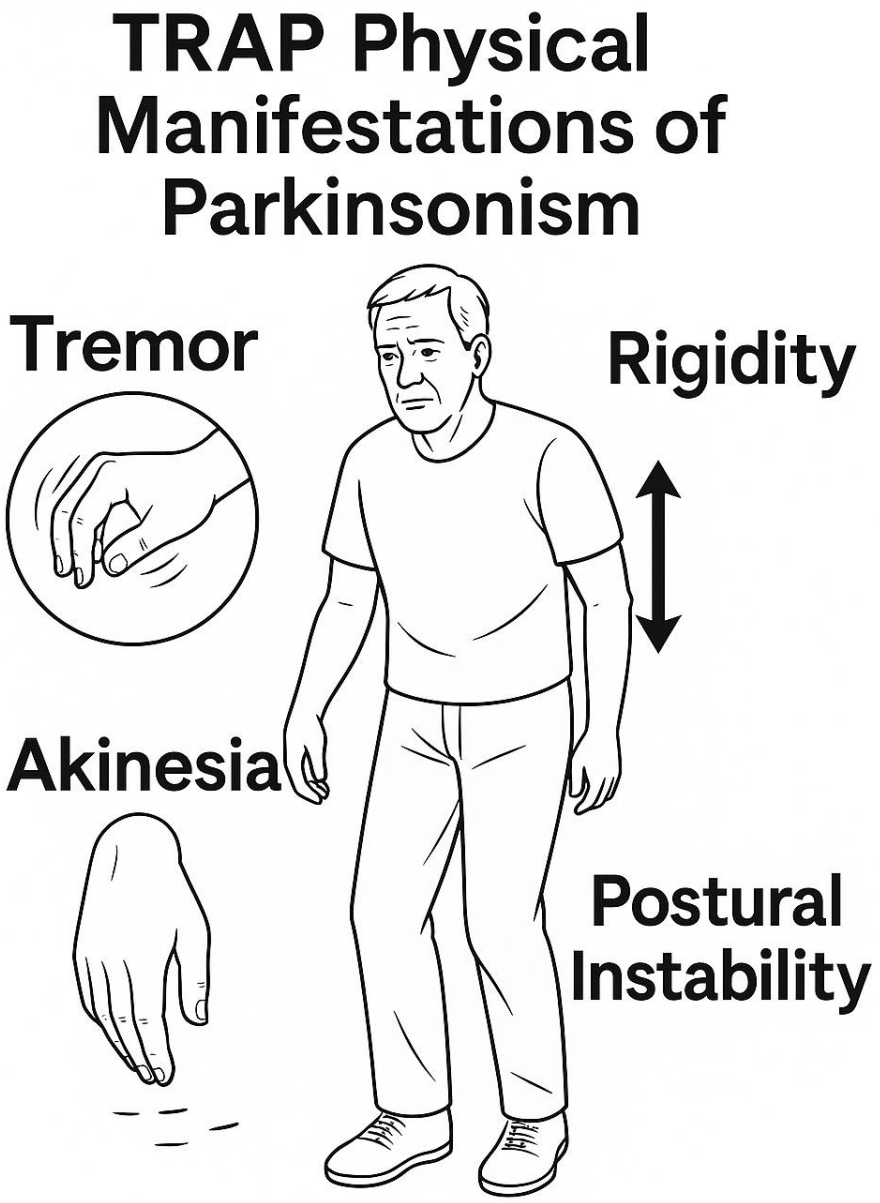
PMHx: constipation, sleep disturbance x 10 years (spouse now in a different bedroom), HTN (diet)

No medications

On exam:

- Increased tone in his upper extremities bilaterally
- Movements are slow (eg. finger tapping)
- Very unstable sit -> stand

Parkinsonism



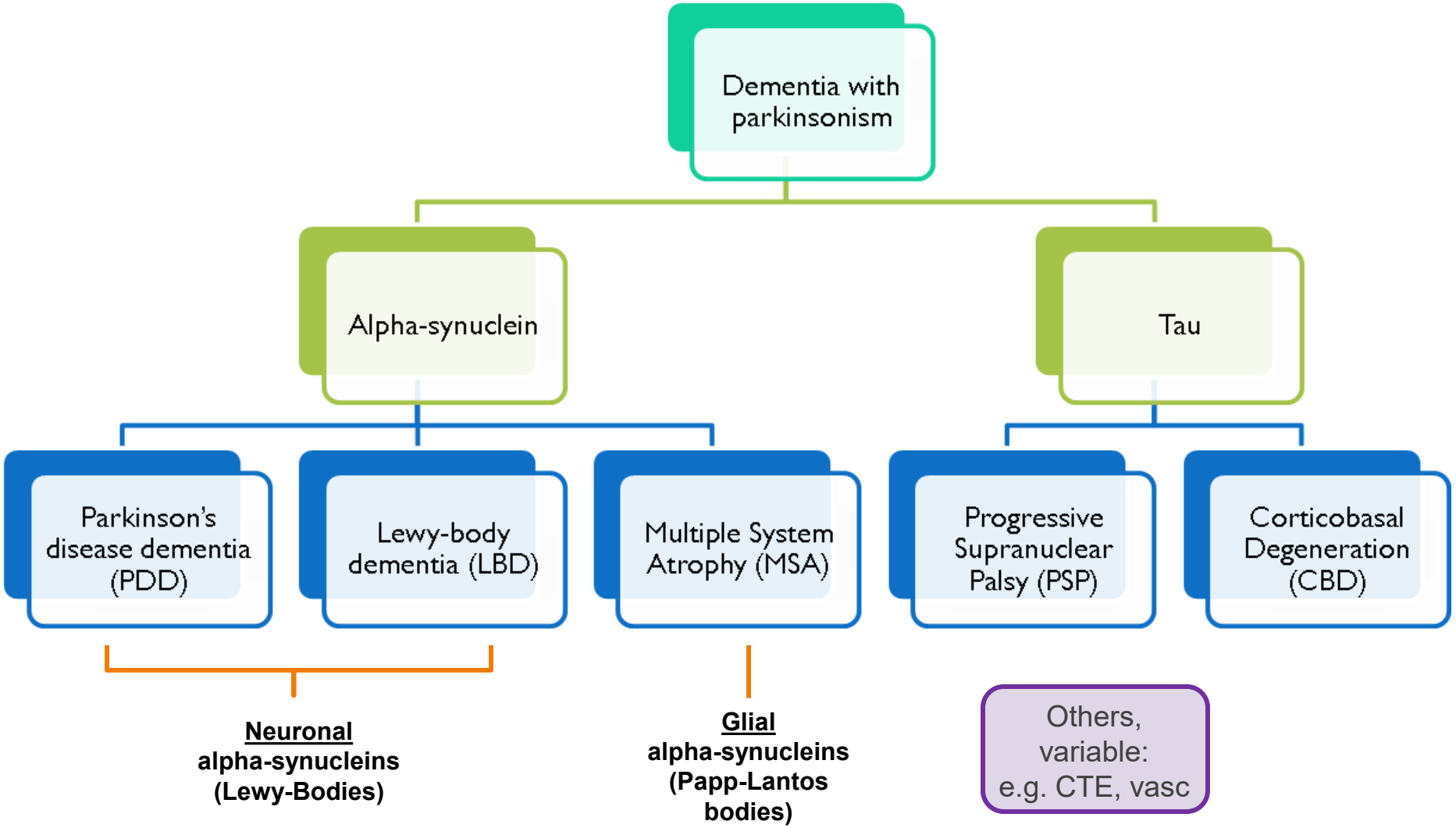
Causes of Parkinsonism

- iPD
- **Parkinson's Plus: PSP, MSA, CBD, LBD**
- Vascular
- CTE
- Advanced dementia
- Infectious (prion dz, encephalitis etc)
- Structural (tumour, AVM, SDH, NPH)
- Metabolic (cirrhosis, Wilson's)
- Meds:
  - Eg. Anti-psychotics (e.g. haldol, phenothiazines)
- Toxins: manganese dust, cyanide, severe CO poisoning

Parkinson's Plus Sx

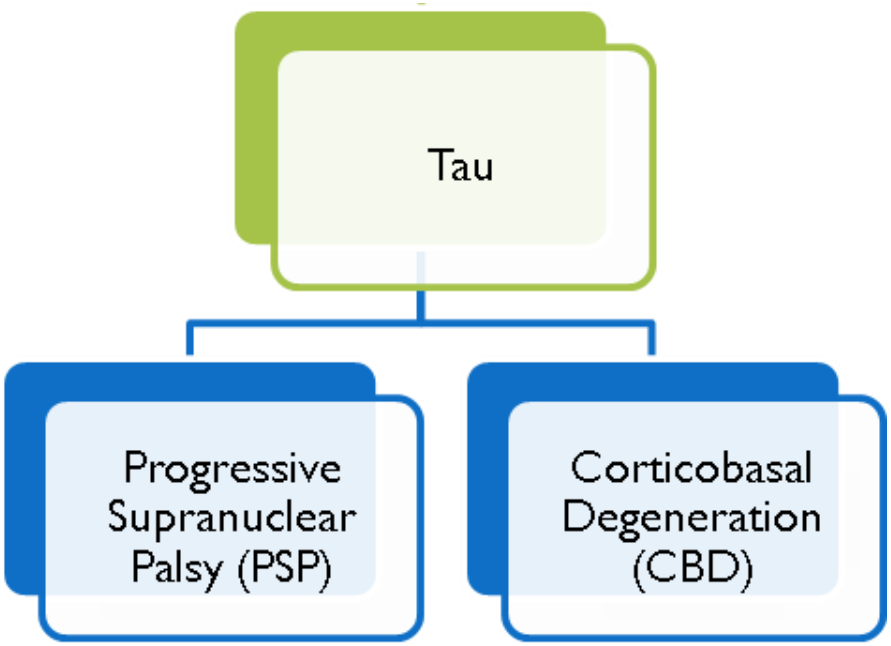
- All are progressive neurodegenerative diseases
- All have some features of parkinsonism and cognitive impairment
- Comparatively rapid progression compared to idiopathic Parkinson's disease
- Poor response to levodopa (main iPD medication)

Dementias with early parkinsonism



Spreading alpha-synucleins cause motor dysfunction and neuronal death

Taupathies


Tau
Progressive Supranuclear Palsy (PSP)
Corticobasal Degeneration (CBD)

PSP

Onset: late 50s-60s, avg 65

Clinical Manifestations:

- Early and frequent falls, often backward
- Vertical gaze palsy (especially downgaze), PSP “stare”
- Axial rigidity > limb rigidity
- Dysarthria, dysphagia
- Executive dysfunction, apathy, emotional lability

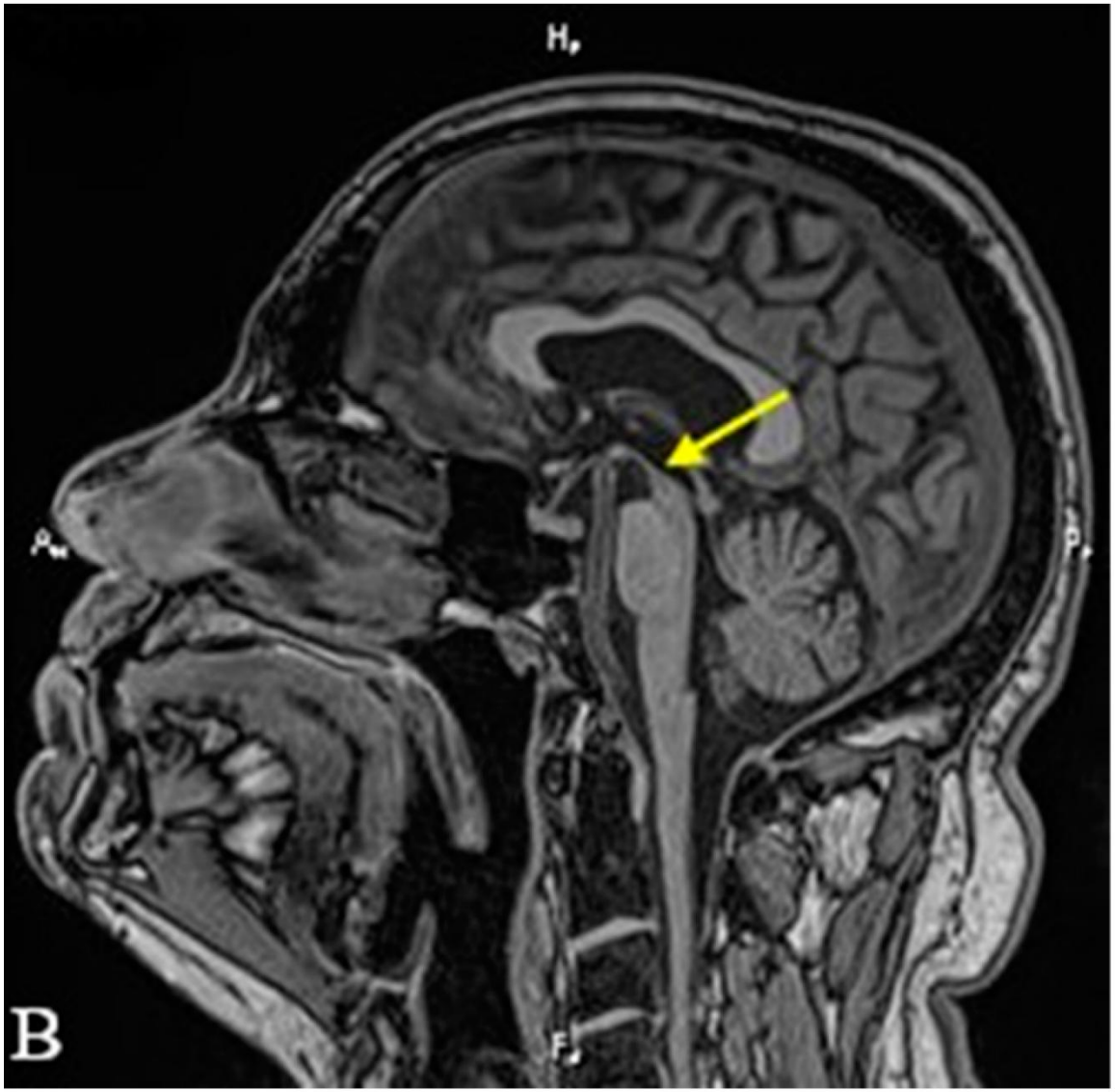
PSP

Physical Exam Findings:

- Impaired voluntary vertical downgaze
  - **+LR 60 for PSP**
- Square wave jerks
- Broad-based, stiff gait with postural instability
- Surprised facial expression, decreased blink rate
- Retrocollis (neck extension/hypertonia)

Genetic testing? Sporadic, no readily available testing

PSP on MRI – Hummingbird Sign



CBD

Onset: often earlier onset, 50s-70s, avg 60-64

Clinical Manifestations:

- Asymmetric parkinsonism, dystonia, myoclonus
- Executive dysfunction, apraxia
- Alien limb
- Aphasia (nonfluent/agrammatic)

CBD

Physical Exam Findings:

- Asymmetric rigidity and bradykinesia
- Limb apraxia: difficulty performing learned tasks
- Cortical sensory loss: astereognosis, agraphesthesia
- Alien limb movements
- Dystonic limb posturing

ASTEREOGNOSIS

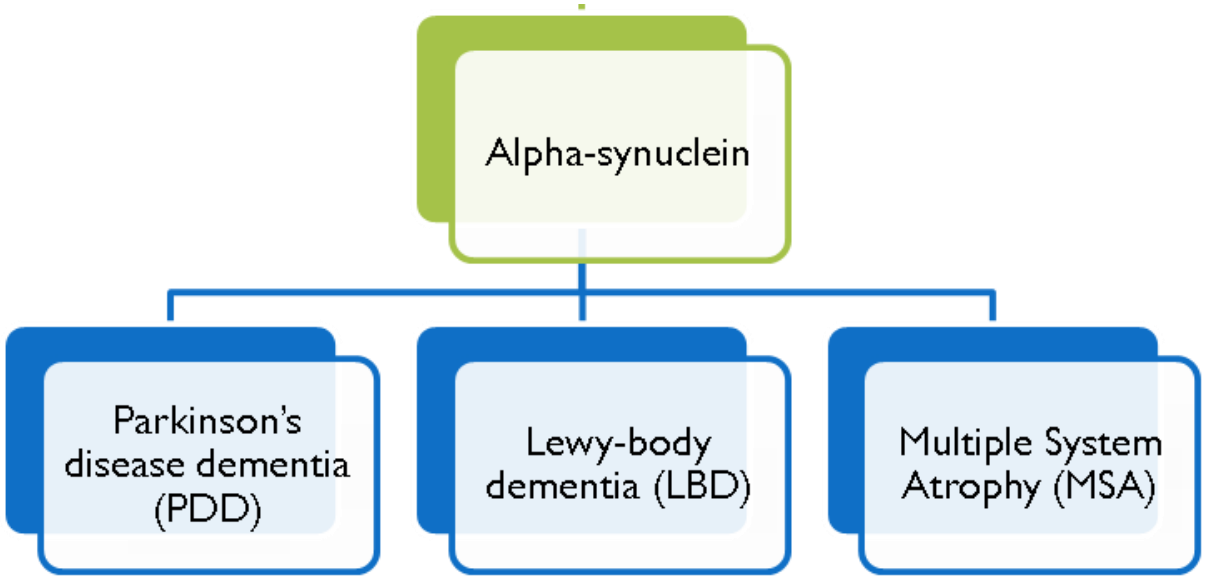
AGRAPHESTHESIA

CBD

MRI findings: asymmetric cortical atrophy

Genetic testing? Sporadic, no readily available testing

Synucleinopathies



MSA

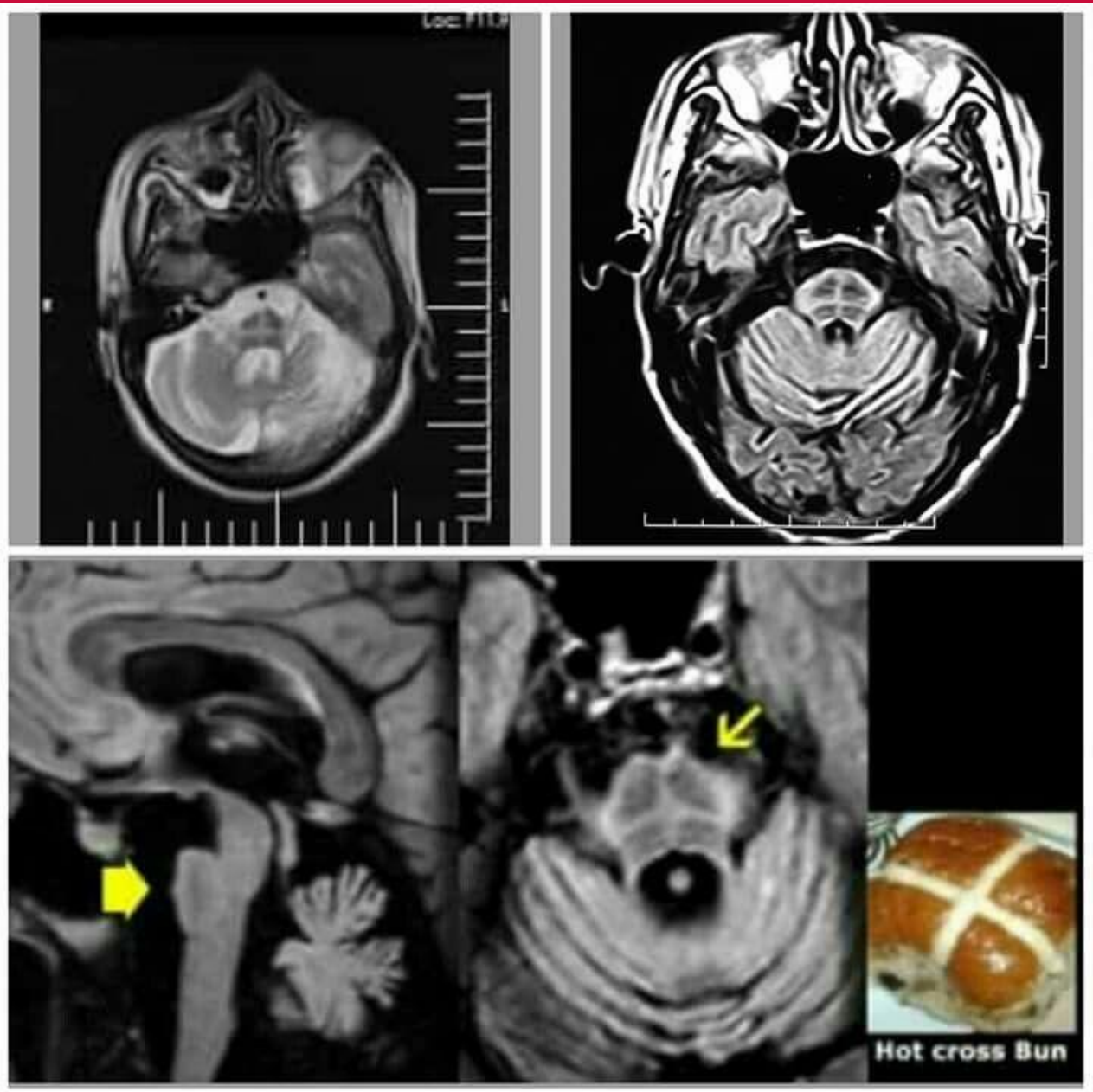
Onset: Young, 50s-60s (avg 54) w/ early onset version < 40

Clinical/Physical Manifestations:

- Progressive cognitive decline, no hallucinations
- Variable degree of parkinsonism (MSA-P)
- Rare to have tremor
- Cerebellar ataxia (MSA-C)
- **Progressive autonomic dysfunction**
  - Severe OH, sBP supine 140 – drops to sBP 60 standing after 3 minutes
  - Urinary incontinence
- Falls falls falls
- Not persistently dopamine responsive

Genetic testing? Usually sporadic, rare family clusters

Hot cross bun sign (pons) on MRI



LBD

- Fairly common (10-30% of cases)
- **Onset:** 50-85, avg 70s
- **Clinical Manifestations:**
  - Visual hallucinations
  - REM behavioural sleep disorder
  - Fluctuating cognition
  - VERY sensitive to anti-psychotics

LBD

- **Physical Exam Findings:**
  - Often rigidity and bradykinesia (less often tremor)

- Overlap with PD but presents with cog/neuropsych before or w/in 1 yr of parkinsonism

- **Genetic testing?** Overlaps with PD risk alleles (SNCA, GBA, APOE variants). Can get medical genetics referral for PD.

Summary of Sx Features

Feature	LBD	MSA	PSP	CBD
Early falls	Less typical	Yes	Very early, backward	Sometimes
EOM	Preserved	Preserved	Vertical palsy	Usually normal
Hallucinations	Common	Rare	Rare	Rare
Autonomic	Possible	Severe, early	Mild	Rare
Symmetry	Symmetric	Symmetric	Symmetric	Markedly asymmetric
Levodopa	Minimal	Minimal	Minimal, sometimes worth a try	Minimal
Unique feature	Cognitive fluctuation, hallucinations	Autonomic dysfunction	Vertical gaze palsy	Alien limb, apraxia

Management

Dopaminergic medications

- Motor: Levodopa is mainstay of treatment for iPD

Table 1. FDA-Approved Medications to Treat Symptoms of Parkinson's Disease

Drug Class	Drug Name
Dopamine precursors	Levodopa
Dopamine agonists	Pramipexole, ropinirole, bromocriptine, pergolide,[a] cabergoline, apomorphine, lisuride, piribedil
COMT inhibitors	Entacapone, tolcapone
MAO-B inhibitors	Selegiline, rasagiline
Anticholinergics	Benztropine, trihexyphenidyl, biperiden
Other	Amantadine

Abbreviations: COMT, catechol-o-methyltransferase; FDA, US Food and Drug Administration; MAO-B, monoamine oxidase isoenzyme type B.
[a] Voluntary US/worldwide market withdrawal in March 2007 due to safety concerns.

COMT inh = prolong effect of levodopa, try to reduce "off" effect
Amantadine (glutamate pathway) = tremor, reduce dyskinesias
MAO-B inh = stops breakdown of dopamine, can help reduce "offs"
Anticholinergics = tremor, reduce dystonias (++ SE)

SE of PD meds

- Dyskinesias
- Multiple SE, can exacerbate:
  - Cognitive impairment
  - Neuropsych symptoms
    - Impulse control d/o (gambling, compulsive shopping, hypersexuality, compulsive eating)
  - Orthostatic HypoTN
  - Daytime somnolence, sleep attacks, nausea, malaise, peripheral edema, etc.

	Evidence in dementia with Lewy bodies	Evidence in Parkinson's disease dementia	Comments
Cognition			
Acetylcholinesterase inhibitors	Efficacious	Efficacious	Rivastigmine and donepezil class 1 efficacy in dementia with Lewy bodies; Cochrane review of dementia with Lewy bodies, Parkinson's disease dementia, and MCI-PD showed overall positive effect
Memantine	Insufficient evidence	Insufficient evidence	Small significant improvement in overall clinical impression
Parkinsonism			
Levodopa	Insufficient evidence	Insufficient evidence	Levodopa replacement less effective in dementia with Lewy bodies than in Parkinson's disease; probable increased risk of psychosis in patients with dementia with Lewy bodies
Hallucinations			
Acetylcholinesterase inhibitors	Insufficient evidence	Insufficient evidence	No randomised controlled trials have assessed hallucinations; other evidence is positive
Antipsychotic drugs	Unlikely to be efficacious	Mixed	In treatment of psychosis associated with Parkinson's disease and Parkinson's disease dementia, clozapine is effective and olanzapine ineffective; the evidence for quetiapine is mixed
Depression or anxiety			
Antidepressant drugs	Insufficient evidence	Insufficient evidence	Evidence mixed; some beneficial effect with venlafaxine, paroxetine, and nortriptyline in Parkinson's disease
RBD			
Melatonin	Insufficient evidence	Insufficient evidence	Evidence in Parkinson's disease from non-randomised trials
Clonazepam	Insufficient evidence	Insufficient evidence	Non-randomised controlled trial evidence positive
Excessive daytime sleepiness			
Modafinil	Insufficient evidence	Insufficient evidence	Evidence in Parkinson's disease from randomised controlled trials; non-randomised trial evidence in dementia with Lewy bodies
Urinary symptoms			
Trospium	Insufficient evidence	Insufficient evidence	No randomised controlled trials reported but does not cross blood–brain barrier so in theory should be preferable to oxybutynin
Postural hypotension			
Fludrocortisone	Insufficient evidence	Insufficient evidence	No evidence from randomised controlled trials, but other evidence positive in both Parkinson's disease dementia and dementia with Lewy bodies

MCI-PD=mild cognitive impairment in Parkinson's disease. RBD=rapid eye movement sleep behaviour disorder.

Table 2: **Evidence for treatment of dementia with Lewy bodies and Parkinson's disease dementia**[125,130]

What if not clear?

Sometimes it is extremely challenging to decide if someone has **iPD vs PSP vs MSA vs LBD vs mixed vs other**

- Especially if you are seeing them late in the disease course
  - E.g. marked postural hypoTN common later in PD, happens much earlier in MSA
- Sinemet trial (dopamine) can be helpful
  - We get pre and post PT measures (TUG, BERG)
  - Try to get to at least 600mg levodopa daily

Treatment of other sx

- Orthostasis:
  - Hydration + salt, compression stockings (up to abdomen)
  - Fludrocortisone, midodrine
  - Non-pharm strategies: slow position changes
- REM:
  - high dose melatonin can be transformative
  - If distressing + melatonin ineffective, trial lowest dose clonazepam at bedtime
- Mood sx: SSRIs +/- CBT if cogn able
- Hallucinations: quetiapine best worst option

Treatment of other sx

- Dementia:
  - Evidence for cholinesterase inhibitors in LBD

Name	Mechanism	Half-life
Donepezil	Acetylcholine inhibitor	70 hours
Galantamine	Acetylcholine inhibitor	7 hours
Rivastigmine	Dual acetylcholine & butyrylcholinesterase inhibitor	1 hour

Note: cholinesterase inhibitors

LBD: can have impressive impact on hallucinations, delusions, and behavioural symptoms

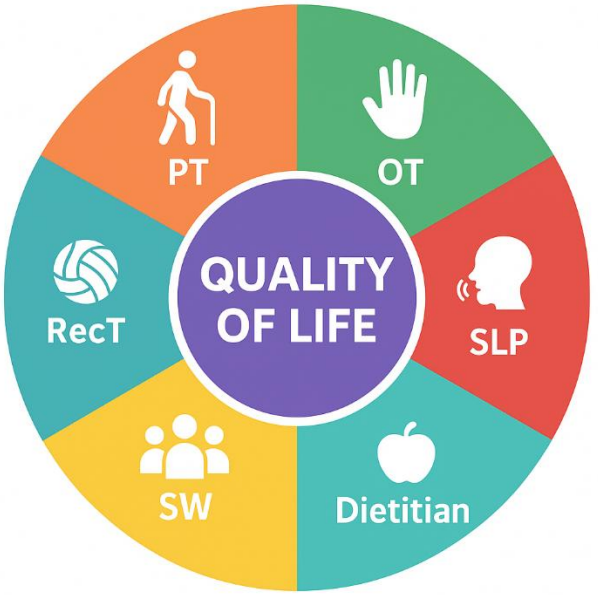
- Can also reduce intensity and frequency of fluctuations
- Some studies suggest a better cognitive response than AD
- Often a robust initial response
- Will eventually stop responding as disease progresses

Non pharmacologic management

Cornerstone of care!

- **PT:** balance and falls prevention, maintenance of strength/endurance, ROM/spasticity in CBD
- **OT:** functional optimization, gait and adaptive aids, home safety/equipment
- **SLP:** dysphagia and dysarthria support
- **RT:** strategies for patient & caregiver
- **SW:** help with accessing resources
- **Dietician:** intake/nutrition

and more!



Back to the case

78M, frequent falls, apathy, visual hallucinations, Capgras, forgetful, can't use the TV remote, moving "slow" + gets "stuck" walking, hard to get out of a chair or turn over in bed, severity of symptoms fluctuate

- Started with hallucinations, cogn 2 years ago, now bradykinesia and rigidity on exam
- Dx LBD
- Rx rivastigmine 1.5mg BID, increase to 3mg BID in 4 weeks -> Capgras resolves!

Take Home Points

1. Suspect Parkinson's Plus when:
   - Poor levodopa response
   - Early falls
   - Early hallucinations
   - Early severe autonomic dysfunction
   - Atypical features (EOM, alien limb)

2. Mostly clinical diagnoses with some MRI findings, no routine genetic testing available/helpful

3. Trial of cholinesterase inhibitors can be considered in LBD, minimal to no role for levodopa

4. Supportive, interdisciplinary care is key to person-centered care

Thank you!

Questions, discussion?