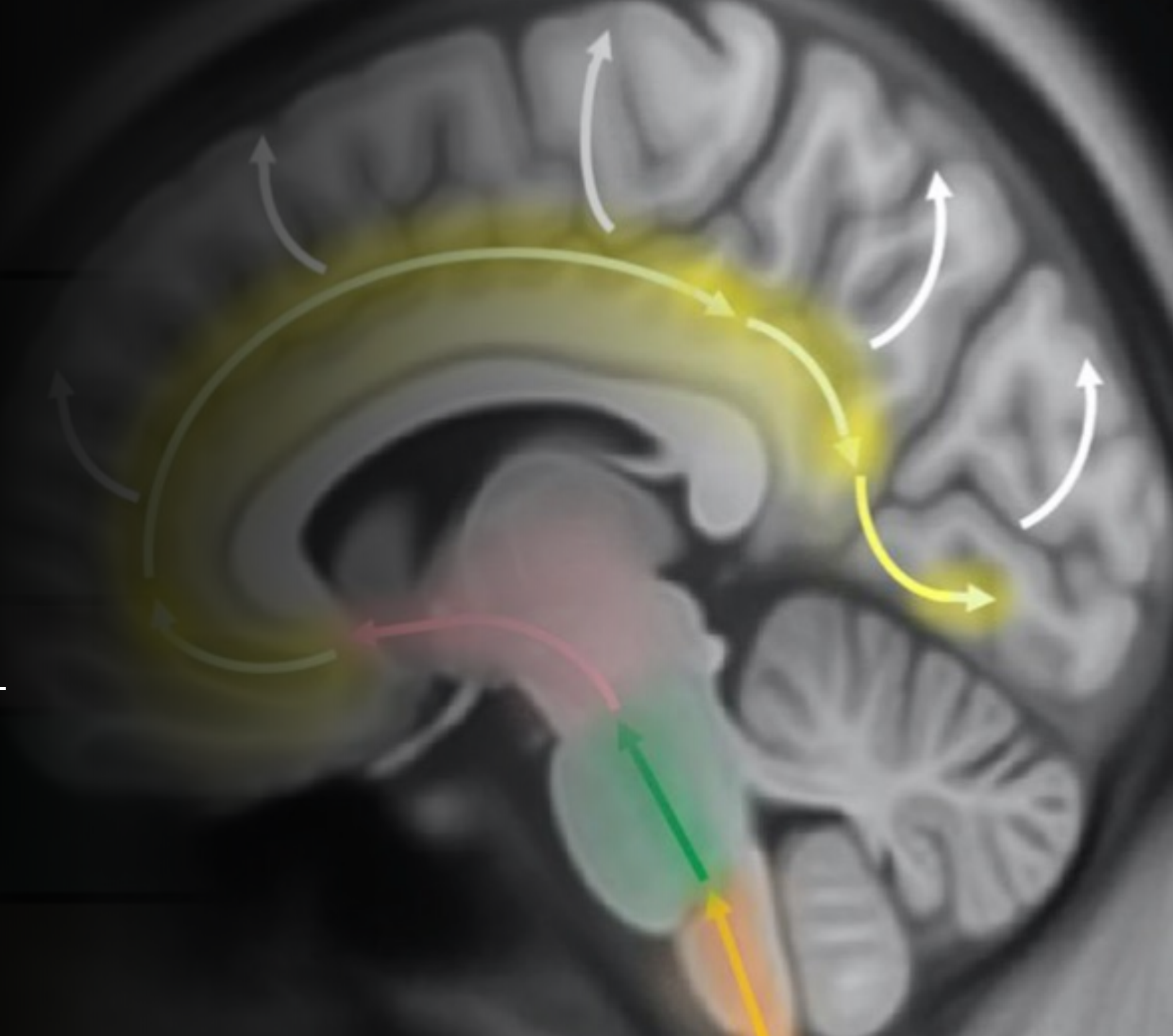
Clinical Pearls in Parkinson's and Parkinson's plus syndromes



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Faculty/Presenter Disclosure

- **Faculty: Camila Aquino, MD**

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Objectives

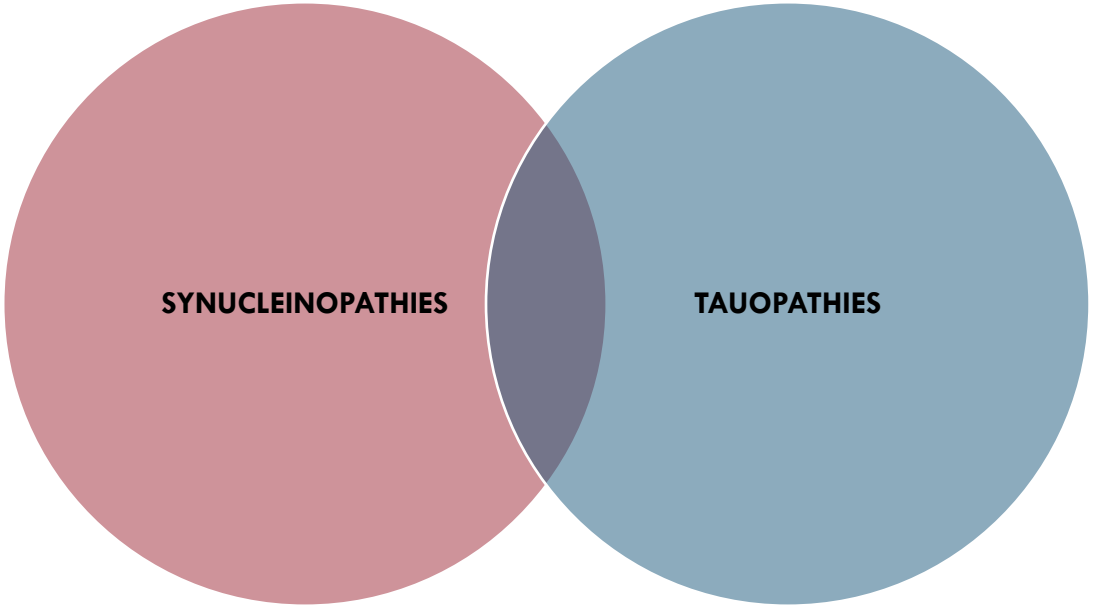
1. To overview the neurodegenerative diseases according to clinicopathological hallmarks
2. To review the common features of synucleinopathies and tauopathies with predominant parkinsonism
3. To review the clinical pearls and updated diagnostic criteria for different parkinsonian syndromes

Parkinsonism

- Parkinsonism is defined as a hypokinetic syndrome and is characterized by the presence of:
  - bradykinesia or akinesia
  - resting tremor
  - muscular rigidity
  - postural instability.

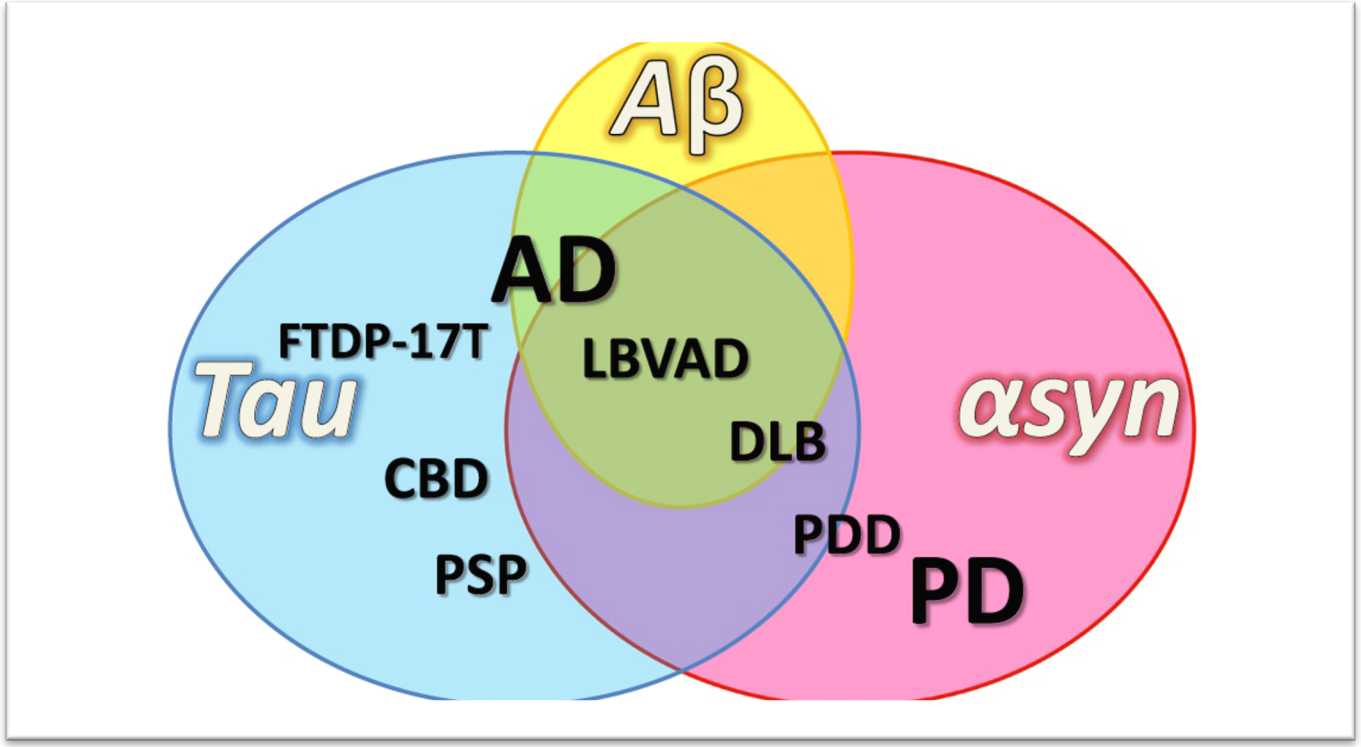
Parkinsonism as clinicopathological entities

- In the past decades, our understanding of neurodegenerative diseases has greatly advanced.
- The realization that accumulation of different abnormal proteins is associated to different brain diseases, has allowed a pathological classification:



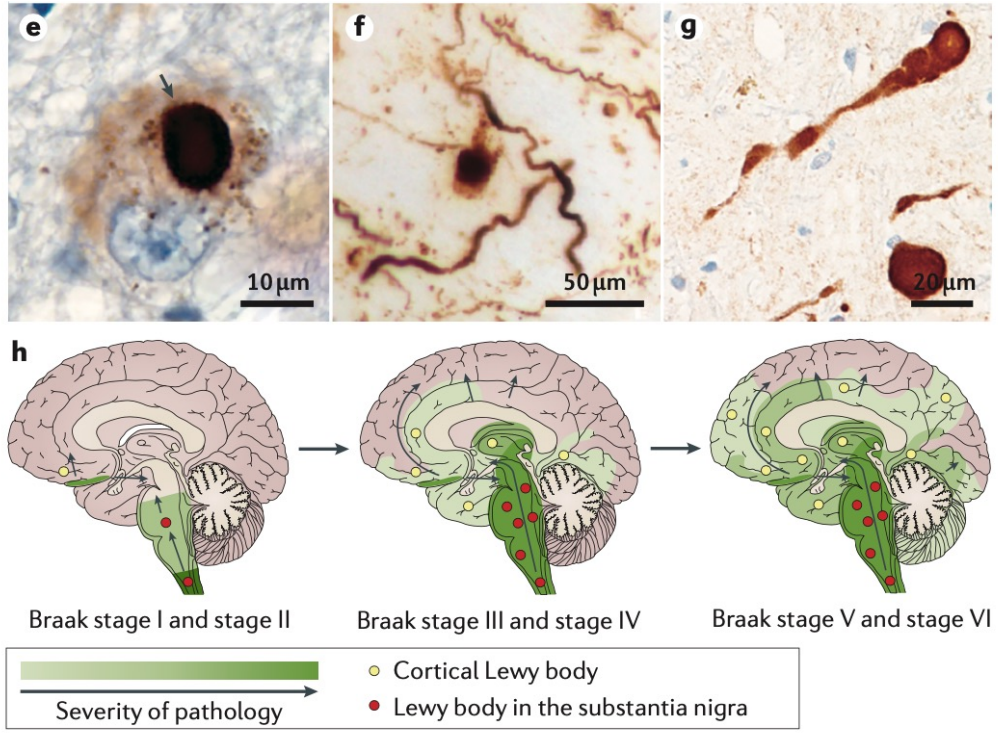
Galpern WR, Lang AE. Interface between tauopathies and synucleinopathies: a tale of two proteins. Ann Neurol. 2006 Mar;59(3):449-58.

- However, there is a substantial overlap between these disorders, at **clinical, pathological, genetic and biochemical levels.**
- These pathologies are not hermetically isolated categories
- It forms a continuum and concomitance with other proteins is not rare (e.g., Aβ, TDP-43)



Alpha-synuclein

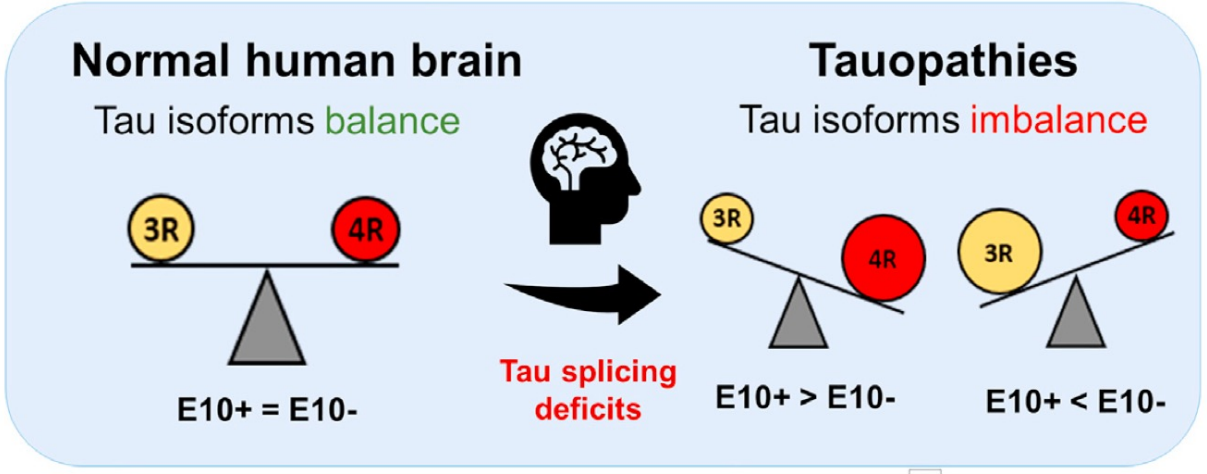
- Structural soluble protein normally present in synapses, and possibly related to synaptic plasticity.
- It is the key component of the **Lewy bodies**



- In 1997: mutation in SNCA gene was linked to an AD form of **PD**.
- a-Synuclein aggregates, including small peptides, oligomers are toxic to the nervous system, and induce a cascade of homeostatic defects, linked to PD.
- a-synuclein insoluble aggregates can be found in neuronal or glial cells.

Poewe W, Seppi K, Tanner CM, et al. Nat Rev Dis Primers. 2017;3(1):17013-17021.

Tau



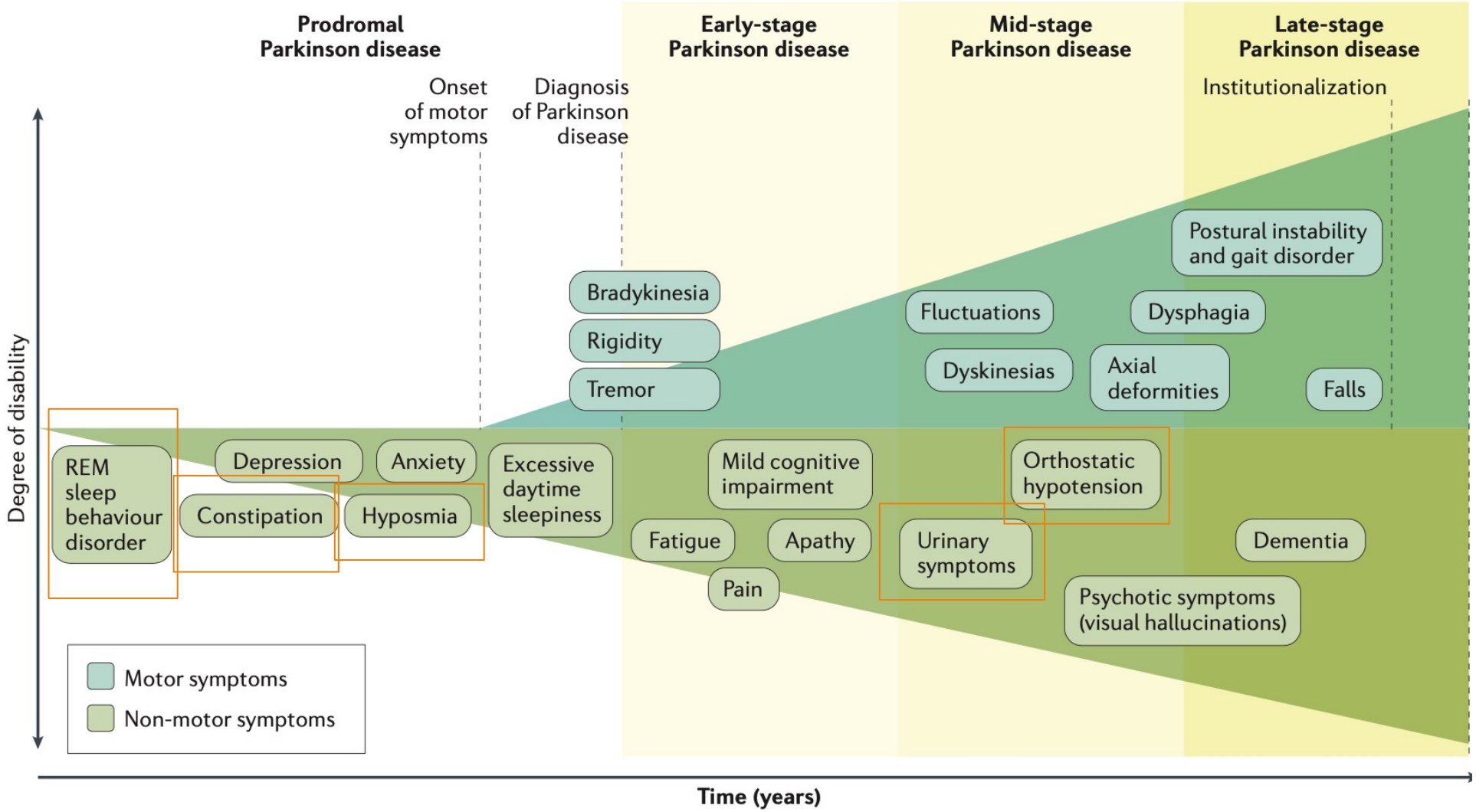
- Microtubule-associated protein involved with axonal transport, encoded by the MAPT gene.
- Hyperphosphorylated tau is polymerized forming neurofibrillary tangles. In AD, brain tau is ~three to four-fold more hyperphosphorylated than the normal adult brain.
- Six different isoforms that differ according to the number of repeats in the microtubule binding region, with a normal equal ratio between 3R and 4R tau.
- **PSP and CBD are tauopathies with preferential accumulation of 4R-tau in neurons and glia.**

Cell Rep. 2018 Apr 17;23(3):709-715.

Parkinsonism associated with Synucleinopathies

- Parkinson's disease (PD)
- Multiple system atrophy (MSA)
- Dementia with Lewy bodies (DLB)

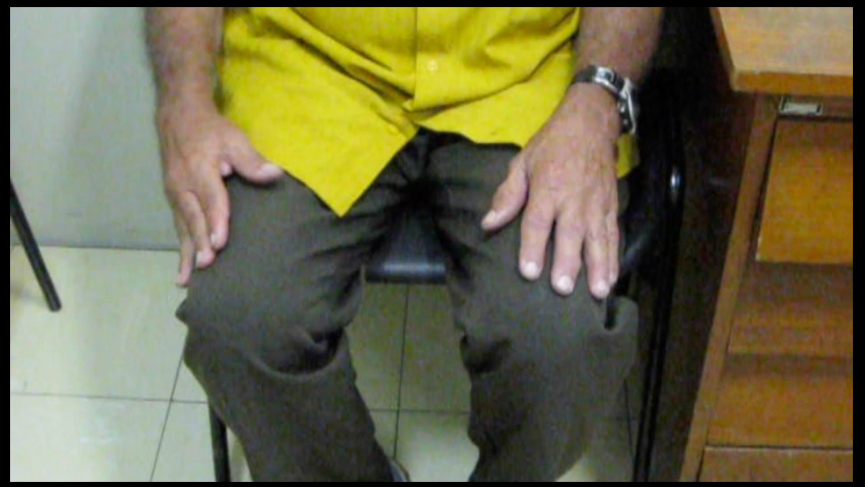
PD as the prototype of synucleinopathy



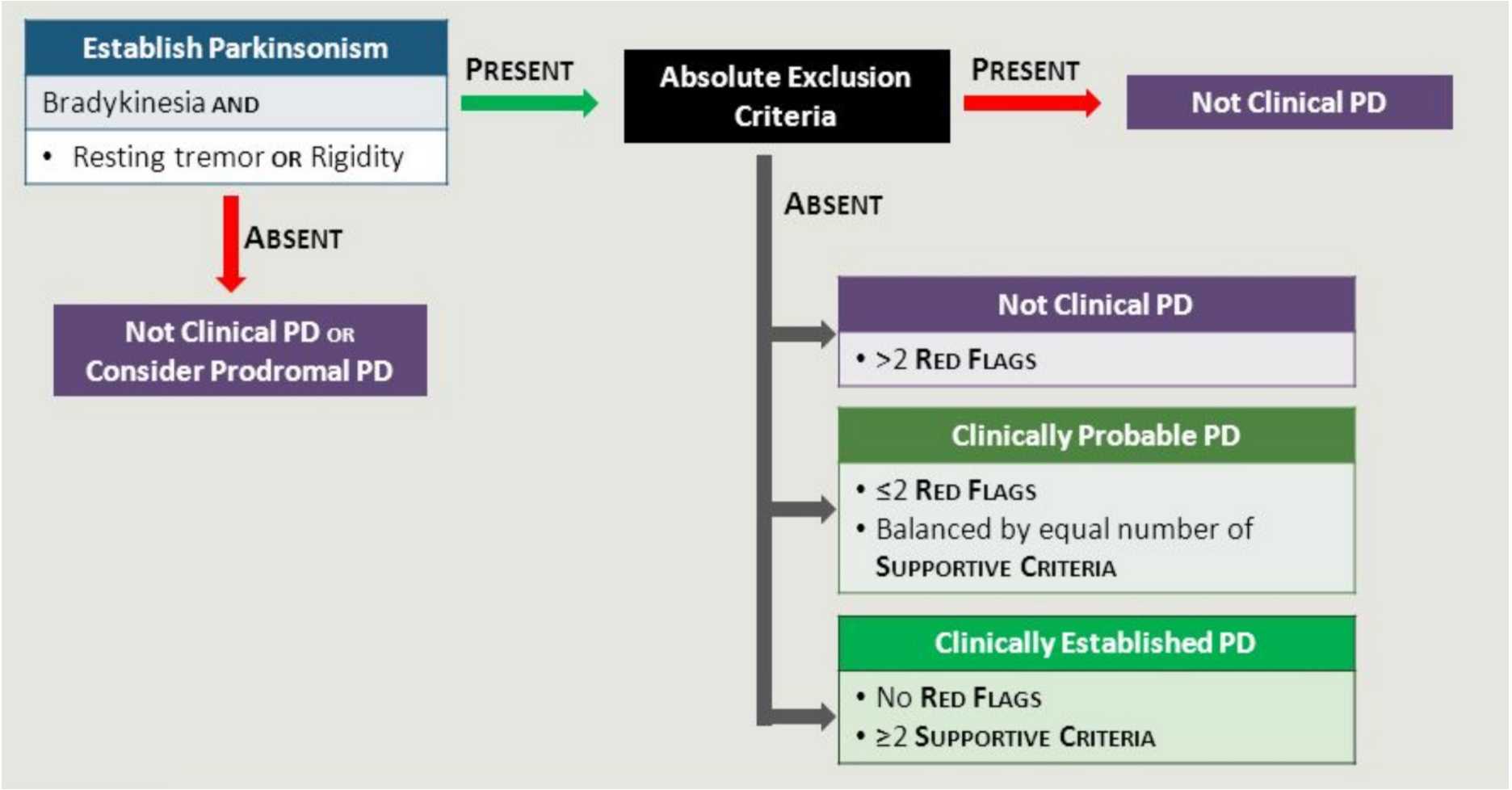
Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. Nat Rev Dis Primers. 2017;3(1):17013-17021.

PD Clinical Pearls

- Slowly progressive disease
- Often preceded by years of prodromal symptoms
- Asymmetric presentation of bradykinesia or resting tremor
- Responsive to levodopa
- Lack of clinically significant postural instability in the initial years
- Lack of significant cortical signs or pyramidal signs



PD Diagnostic Criteria



Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30:1591-1599

Absolute Exclusion Criteria
Unequivocal cerebellar abnormalities
Downward vertical supranuclear palsy or selective slowing of downward vertical saccades
Probable behavioral variant frontotemporal dementia or primary progressive aphasia within 5 years
Parkinsonian features restricted to lower limbs for >3 years
Possible drug-induced parkinsonism
No response to high-dose levodopa despite at least moderate disease
Unequivocal cortical sensory loss, limb ideomotor apraxia, or progressive aphasia
Normal functional neuroimaging of presynaptic dopaminergic system, if performed
Parkinsonism due to an alternative condition

Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30:1591-1599

Red Flags
Rapid progression of gait impairment requiring wheelchair within 5 years
Absence of motor progression over ≥5 years unless stabilized on treatment
Early bulbar dysfunction within 5 years
Inspiratory respiratory dysfunction
Severe autonomic failure within 5 years including • Orthostatic hypotension • Severe urinary incontinence or retention
>1 falls per year because of impaired balance within 3 years
Disproportionate anterocollis or contractures of hands or feet within 10 years
Absence of any common nonmotor features of PD despite 5 years of disease duration, including • Sleep dysfunction • Autonomic dysfunction • Hyposmia • Psychiatric dysfunction
Unexplained pyramidal tract signs, excluding mild reflex asymmetry and isolated extensor plantar response

Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30:1591-1599

Supportive Criteria
Unequivocal and dramatic response to dopaminergic treatment
Levodopa-induced dyskinesia
Resting tremor
Positive ancillary testing • Olfactory loss • MIBG scintigraphy demonstrating cardiac sympathetic denervation

Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30:1591-1599

True or false? Please, respond in the chat.

- Autonomic dysfunction, including significant orthostatic hypotension that requires pharmacological intervention is considered an exclusion criteria for PD.

Multiple System Atrophy

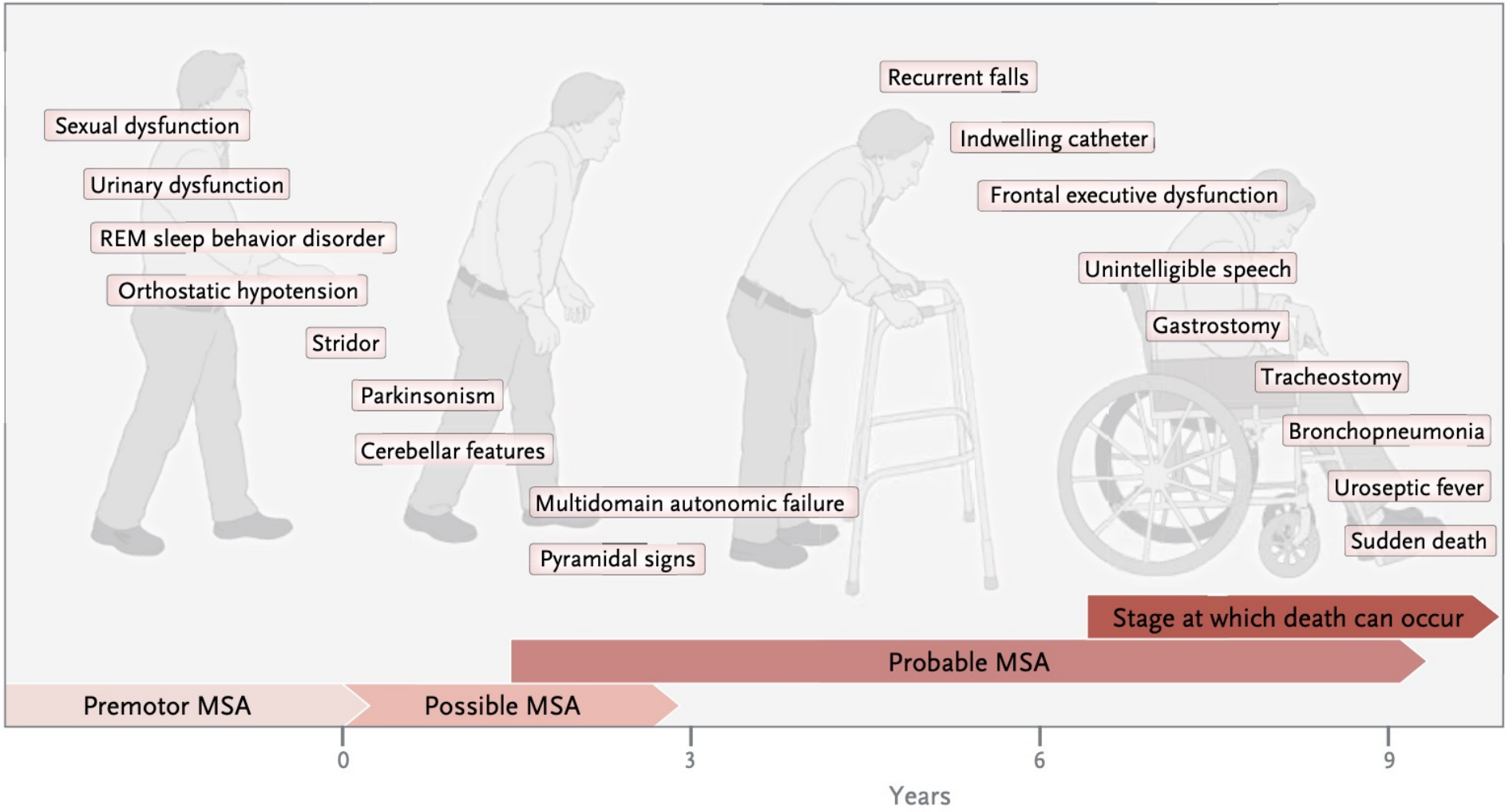
- MSA is a synucleinopathy characterized by progressive autonomic failure, parkinsonian features, and cerebellar and pyramidal features in various combinations.
- Median age of onset is 58 years of age
- Mean survival is approximately 6 to 9 years.

Clinical Presentation	Features[a]
Multiple system atrophy–parkinsonian type (MSA-P) (previously referred to as Shy-Drager syndrome or striatonigral degeneration)	Onset >40 years, duration <10 years, progressive parkinsonism poorly responsive to levodopa, with autonomic failure (including orthostatic hypotension, impotence, bladder dysfunction)
Multiple system atrophy–cerebellar type (MSA-C) (previously referred to as olivopontocerebellar atrophy)	Ataxia; degeneration of ventral pons, olives, cerebellum; mild parkinsonism and cognitive decline

[a] Autonomic dysfunction, respiratory symptoms, and sleep disturbance can precede motor signs by months to years.

McFarland NR. Continuum. 2016;22:1117-1142.

MSA Timeline



Fanciulli A, Wenning GK. Multiple-System Atrophy. N Engl J Med. 2015;372(3):249-263.

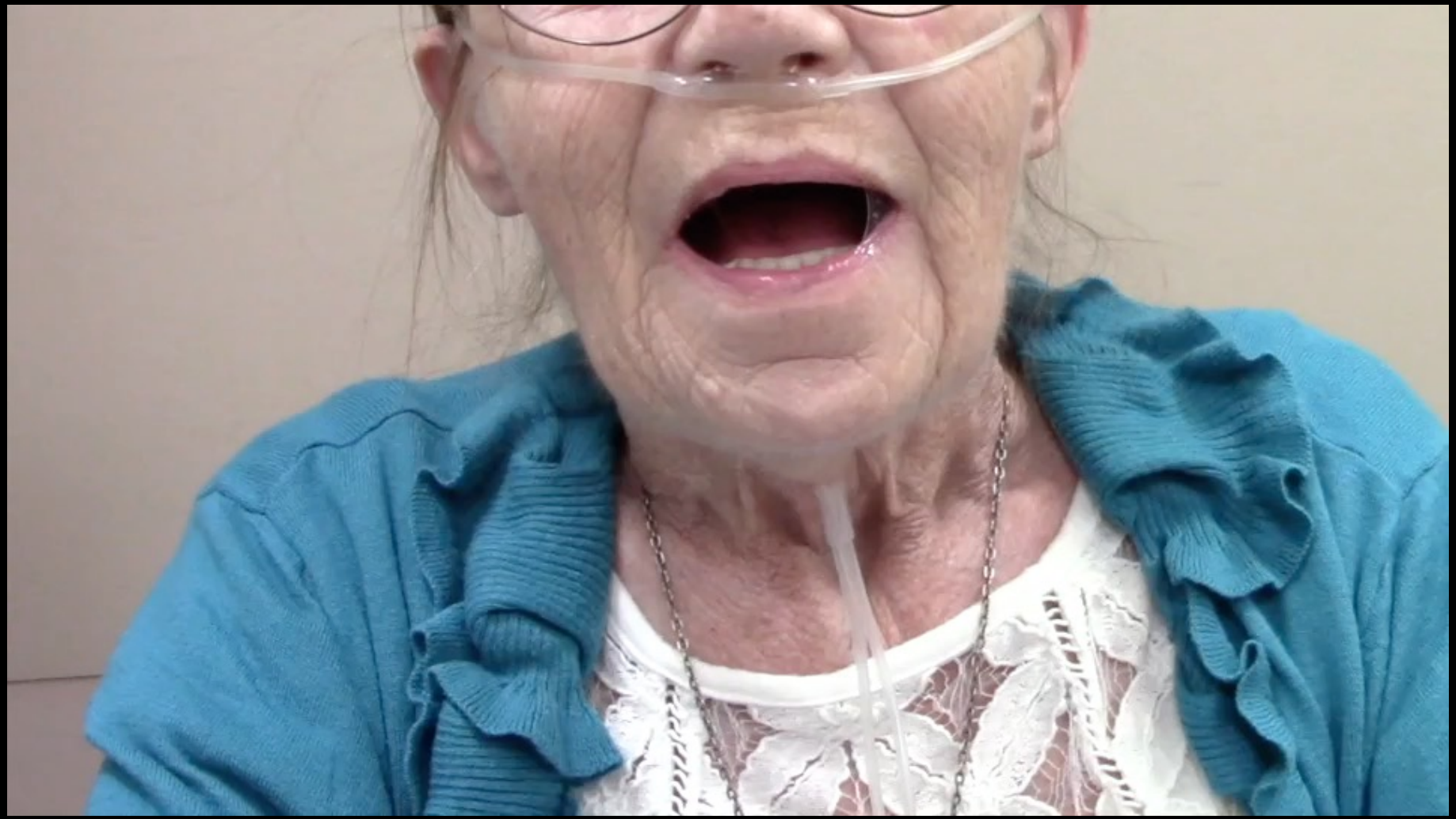
Clinical Pearls in MSA

Parkinsonism: more symmetric but can also be asymmetric. Pill-rolling tremor is uncommon. Often there is a postural component of myoclonic jerks, irregular and with small amplitude. Tongue tremor common. Anterocollis and camptocormia.

Cerebellar features: consist of a wide-based gait, uncoordinated limb movements, action tremor, and spontaneous, gaze-evoked, or positional downbeat nystagmus.

Autonomic dysfunction: Orthostatic hypotension (>30 mmHg drop systolic/15 diastolic); genitourinary dysfunction ED, urgency/frequency, retention, constipation, diarrhea, thermoregulatory failure, absent sweating.

Respiratory disorders: nocturnal or diurnal stridor, sleep apnea, aspiration pneumonia (dysphagia).



MSA Diagnostic criteria

Table 1 **Criteria for the diagnosis of probable MSA**

A sporadic, progressive, adult (>30 y)–onset disease characterized by
• Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic *and*
• Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) *or*
• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

Table 2 **Criteria for possible MSA**

A sporadic, progressive, adult (>30 y)–onset disease characterized by
• Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) *or*
• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) *and*
• At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) *and*
• At least one of the additional features shown in table 3

Second consensus statement on the diagnosis of multiple system atrophy. In: Vol 71. 2008:670-676.

MSA Diagnostic criteria

Table 3 **Additional features of possible MSA**

Possible MSA-P or MSA-C
• Babinski sign with hyperreflexia
• Stridor
Possible MSA-P
• Rapidly progressive parkinsonism
• Poor response to levodopa
• Postural instability within 3 y of motor onset
• Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
• Dysphagia within 5 y of motor onset
• Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
• Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
Possible MSA-C
• Parkinsonism (bradykinesia and rigidity)
• Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
• Hypometabolism on FDG-PET in putamen
• Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

MSA = multiple system atrophy; MSA-P = MSA with predominant parkinsonism; MSA-C = MSA with predominant cerebellar ataxia; FDG = [^{18}F]fluorodeoxyglucose.

Second consensus statement on the diagnosis of multiple system atrophy. In: Vol 71. 2008:670-676.

MSA Diagnostic criteria

Table 4 **Features supporting (red flags) and not supporting a diagnosis of MSA**

Supporting features	Nonsupporting features
• Orofacial dystonia	• Classic pill-rolling rest tremor
• Disproportionate antecollis	• Clinically significant neuropathy
• Camptocormia (severe anterior flexion of the spine) and/or Pisa syndrome (severe lateral flexion of the spine)	• Hallucinations not induced by drugs
• Contractures of hands or feet	• Onset after age 75 y
• Inspiratory sighs	• Family history of ataxia or parkinsonism
• Severe dysphonia	• Dementia (on DSM-IV)
• Severe dysarthria	• White matter lesions suggesting multiple sclerosis
• New or increased snoring	
• Cold hands and feet	
• Pathologic laughter or crying	
• Jerky, myoclonic postural/action tremor	

Second consensus statement on the diagnosis of multiple system atrophy. In: Vol 71. 2008:670-676.

True or false? Please, respond in the chat.

- A good response to levodopa is considered an exclusion criteria for Multiple System Atrophy?

Dementia with Lewy Bodies

- Defined as an **early-onset, rapidly progressive dementia** that is part of the spectrum of PD.
- in addition to:
    - parkinsonism that is coincident with or follows dementia onset
    - fluctuating cognition, awareness, or alertness
    - recurrent visual hallucinations.
- Other symptoms include: gait instability, falls, syncope or transient loss of consciousness, delusions/paranoia, depression, REM sleep behavior disorder, excessive daytime sleepiness, and neuroleptic sensitivity.

Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. J Neural Transm. 2017;125(4):615-650.

Clinical Pearls in DLB

Parkinsonism: either bradykinesia, rigidity, or postural instability. Typical PD tremor is uncommon.

Hallucinations: Early, in comparison to PD. Visual content, well-formed, featuring people, children, or animals, sometimes accompanied by passage hallucinations, sense of presence, and visual illusions.

Cognitive Fluctuations: waxing and waning episodes of behavioral inconsistency, incoherent speech, variable attention, or altered consciousness that involves staring or zoning out, particularly at early stages.

DLB Diagnostic Criteria

Table 3. Revised criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB) (2017)

- **Central feature**: *Essential for a diagnosis of DLB*

  Dementia. In the early stages, prominent memory impairment may not occur, but deficits of attention, executive function, and visuoperceptual ability may be prominent.

- **Core clinical features** (The first 3 typically occur early and may persist throughout the course)
  - Fluctuating cognition with pronounced variations in attention and alertness
  - Recurrent visual hallucinations that are typically well formed and detailed
  - Rapid eye movement (REM) sleep behavior disorder (RBD), which may precede cognitive decline
  - One or more spontaneous cardinal features of parkinsonism: bradykinesia, resting tremor, or rigidity

- **Supportive clinical features**

  Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction (e.g., constipation, orthostatic hypotension, or urinary incontinence); hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; and apathy, anxiety, and depression

Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017;89(1):88-100.

DLB Diagnostic Criteria

○ **Indicative biomarkers**

- Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT/PET
- Abnormal (low uptake) ^{123}I-MIBG myocardial scintigraphy
- Polysomnographic confirmation of REM sleep without atonia

○ **Supportive biomarkers**

A relative preservation of medial temporal lobe structures on CT/MRI scan; generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging; prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range

Probable DLB

a. Two or more core clinical features are present, or

b. Only one core clinical feature is present, but with one or more indicative biomarkers

Possible DLB

a. Only one core clinical feature, or

b. One or more indicative biomarkers is present, but there are no core clinical features

Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017;89(1):88-100.

True or false? Please, respond in the chat.

- A patient with dementia, with cognitive fluctuations and RBD, can only be diagnosed with DLB if two or more signs of parkinsonism are present?

Parkinsonism associated with Tauopathies

- **Progressive supranuclear palsy**
- **Corticobasal degeneration**
- Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTPD-17)
- Parkinsonism-dementia complex of Guam
- Postencephalitic parkinsonism
- Dementia pugilistica

Progressive supranuclear palsy

- PSP is a ‘pure tauopathy’, where tau accumulations composed primarily of 4R tau species
- average age of onset is around the mid- 60s
- disease duration is approximately 6 years
- The classical phenotype, described Richardson-Steele-Olszewski is characterized by onset of postural instability, falls, supranuclear gaze palsy, axial rigidity and dementia.
- Over the years, several clinical phenotypes have been identified:

Coughlin DG, Litvan I. Progressive supranuclear palsy: Advances in diagnosis and management. Parkinsonism and Related Disorders. 2020;73:105-116.

PSP Clinical phenotypes

Progressive Supranuclear Palsy (PSP) Syndrome	Clinical Features	Regional Pathology
Classic PSP (Richardson syndrome)	Early gait instability, falls, supranuclear gaze palsy, axial rigidity, dysarthria, dysphagia, progressive dementia	Dentate nucleus, globus pallidus, striatum, midbrain, and superior cerebellar peduncle
PSP-parkinsonism	Tremor, rigid bradykinesia, levodopa responsive,[a] late cognitive decline, longer life expectancy (9 years)	Substantia nigra, subthalamic nucleus
PSP–pure akinesia with gait freezing	Early gait difficulty, freezing of gait/motor block, micrographia, speech impairment, hypophonia, longer disease duration (11–15 years)	Motor cortex, pons, cerebellum
PSP–corticobasal syndrome	Dystonia, dyspraxia, cortical sensory loss, apraxia of speech	Frontal and parietal cortex
PSP–behavioral variant of frontotemporal dementia	Predominant cognitive, personality change, late parkinsonism	Frontotemporal cortex
PSP–primary lateral sclerosis	Bulbar, limb weakness, upper motor neuron signs/spasticity	Frontal predominant, corticospinal tract
PSP-cerebellar	Cerebellar ataxia	Deep cerebellar nuclei

[a] Levodopa response for PSP-parkinsonism wanes later in disease.

Clinical Pearls in PSP

Parkinsonism tends to be symmetrical, except in PSP-P, where it can be very similar to PD.

Axial rigidity, can be detected in the neck and trunk.

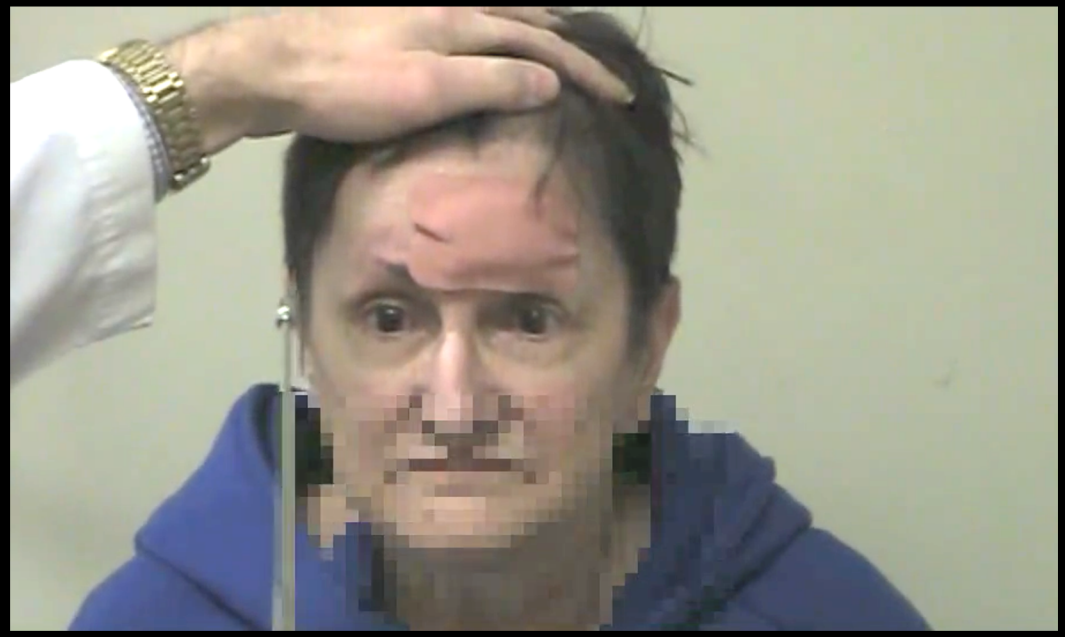
Slow saccades, abnormal vertical OKN. Eyelid opening apraxia.

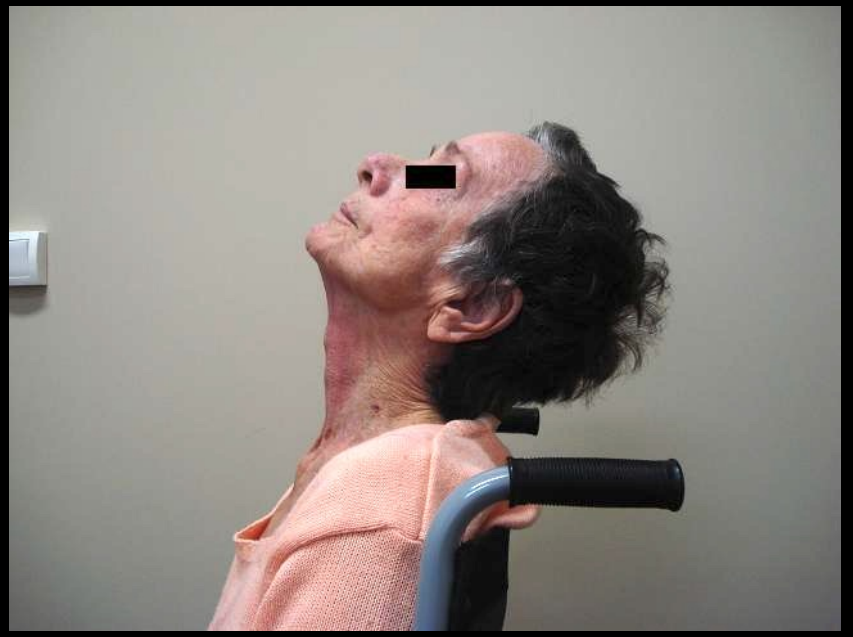
Disproportionate neck extension – retrocollis, and often straight/erect posture, as opposed to PD or MSA.

Early dysarthria, slurred speech.

Frontal release signs: applause sign, grasp, snout.

Very poor responsive to levodopa.





PSP Diagnostic Criteria

Mandatory:

1. Sporadic occurrence
2. 2. Age 40 or older at onset of first PSP-related symptom
3. Gradual progression of PSP-related symptoms

	Functional Domain			
Levels of Certainty	Ocular Motor Dysfunction	Postural Instability	Akinesia	Cognitive Dysfunction
Level 1	**O1**: Vertical supranuclear gaze palsy	**P1**: Repeated unprovoked falls within 3 years	**A1**: Progressive gait freezing within 3 years	**C1**: Speech/language disorder, i.e., nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech
Level 2	**O2**: Slow velocity of vertical saccades	**P2**: Tendency to fall on the pull-test within 3 years	**A2**: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	**C2**: Frontal cognitive/behavioral presentation
Level 3	**O3**: Frequent macro square wave jerks or "eyelid opening apraxia"	**P3**: More than two steps backward on the pull-test within 3 years	**A3**: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	**C3**: Corticobasal syndrome

Sources

Clinical diagnosis of progressive supranuclear palsy: The MDS criteria. Mov Disord. 2017;32(6):853-864.

PSP Diagnostic Criteria

Supportive features	Exclusion criteria
Levodopa resistance	Impaired episodic memory suggestive of AD
Hypokinetic, spastic dysarthria	Autonomic failure
Dysphagia	Visual hallucinations or fluctuations in alertness
Photophobia	Lower and upper motor neuron signs like ALS
Imaging:	Sudden onset
Predominant midbrain atrophy or hypometabolism	Encephalitis
Postsynaptic striatal dopaminergic degeneration	Ataxia
	Other causes for postural instability – vestibular, spasticity, sensory deficits.

Clinical diagnosis of progressive supranuclear palsy: The MDS criteria. Mov Disord. 2017;32(6):853-864.

Corticobasal degeneration

- "Corticobasal Degeneration" was previously used to describe the clinical syndrome of asymmetric parkinsonism, apraxia, executive and parietal lobe dysfunction currently known as corticobasal syndrome (CBS).
- Findings from autopsy studies in CBS that <50% of CBS patients had CBD neuropathology at autopsy. Alternative findings were AD, PSP, TDP-43 pathology, and others.
- CBD combines markedly asymmetric rigidity and bradykinesia with focal or hemidystonia and cortical deficits.
- Most patients develop symptoms ~ 63 years (45 to 77.2)
- CBD disease duration is ~6.6 years (range 2.0–12.5)
- Dementia is common in CBD.

Tauopathies as clinicopathological entities. Parkinsonism and Related Disorders. 2016;22 Suppl 1:S29-S33.

Clinical Pearls in CBD

Parkinsonism: very asymmetric, usually with no typical resting tremor (but can have myoclonus), with early loss of balance, and no response to levodopa.

Dystonia in one body side, progressive, initially with posturing, but often becoming a fixed deformity.

Speech/language: dysarthria, aphasia and apraxia of speech can occur.

Cortical signs: apraxia, cortical sensory loss (two-point discrimination, agraphesthesia), difficulty recognizing objects by touch alone, cortical myoclonus.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CBD Diagnostic Criteria

Probable CBS

Asymmetric presentation of 2 of:

a) limb rigidity or akinesia

b) limb dystonia

c) limb myoclonus

plus 2 of:

d) orobuccal or limb apraxia

e) cortical sensory deficit

f) alien limb phenomena (more than simple levitation)

Possible CBS

May be symmetric, 1 of:

a) limb rigidity or akinesia

b) limb dystonia

c) limb myoclonus

plus 1 of:

d) orobuccal or limbapraxia

e) cortical sensory deficit

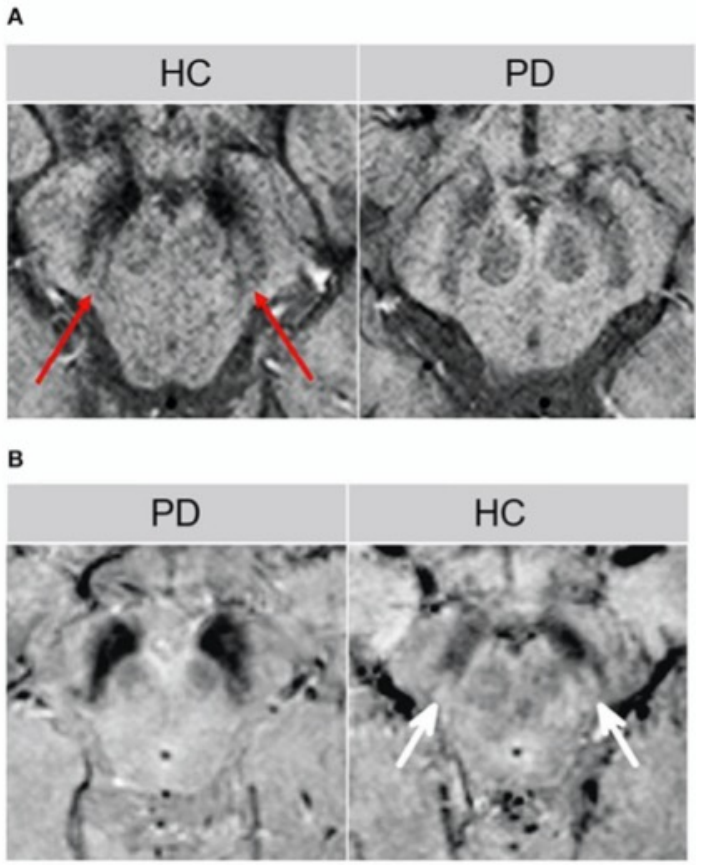
f) alien limb phenomena (more than simple levitation)

Criteria for the diagnosis of corticobasal degeneration.
Neurology 2013, 80 (5) 496-503.

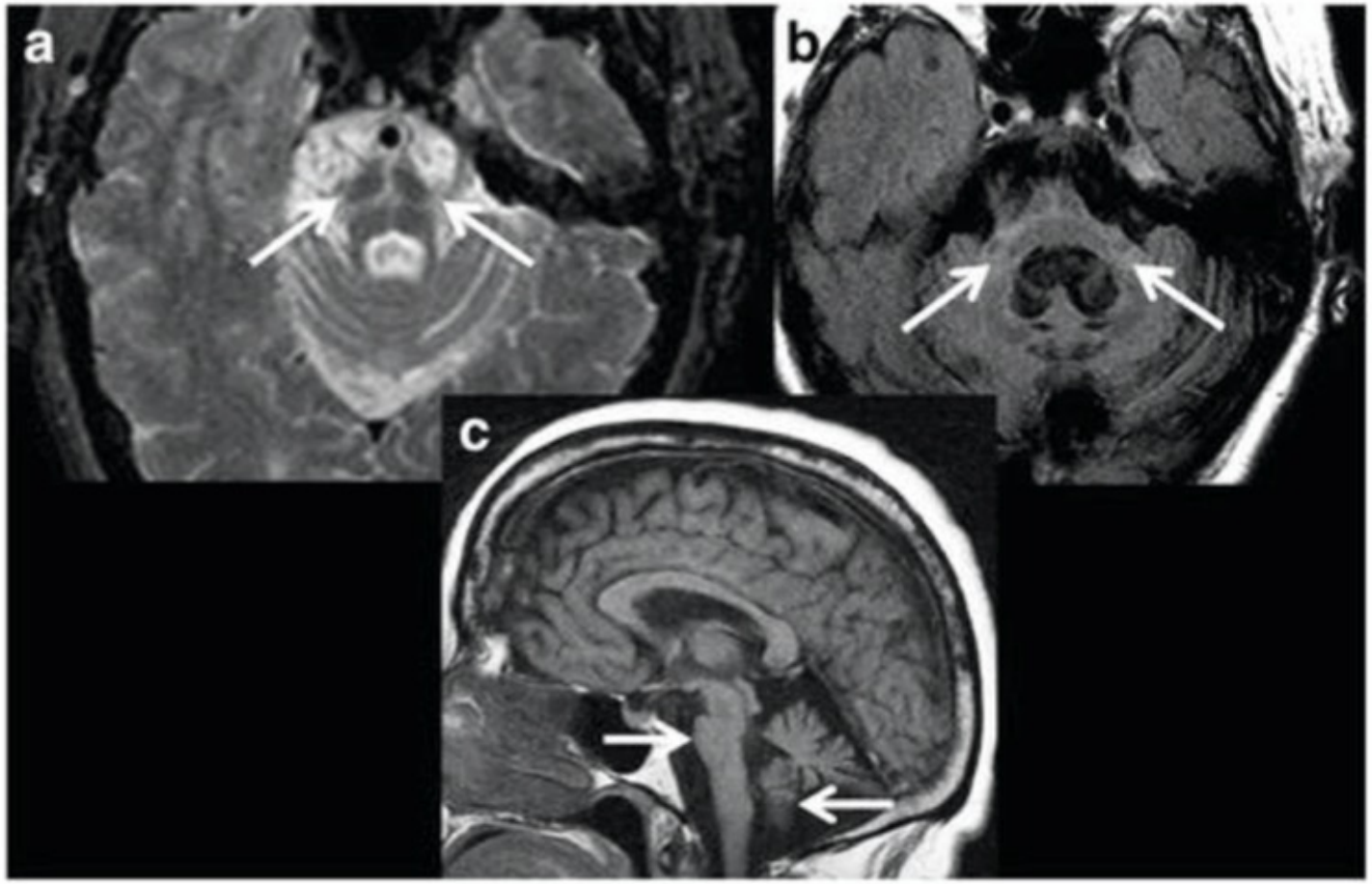
True or false? Please, respond in the chat.

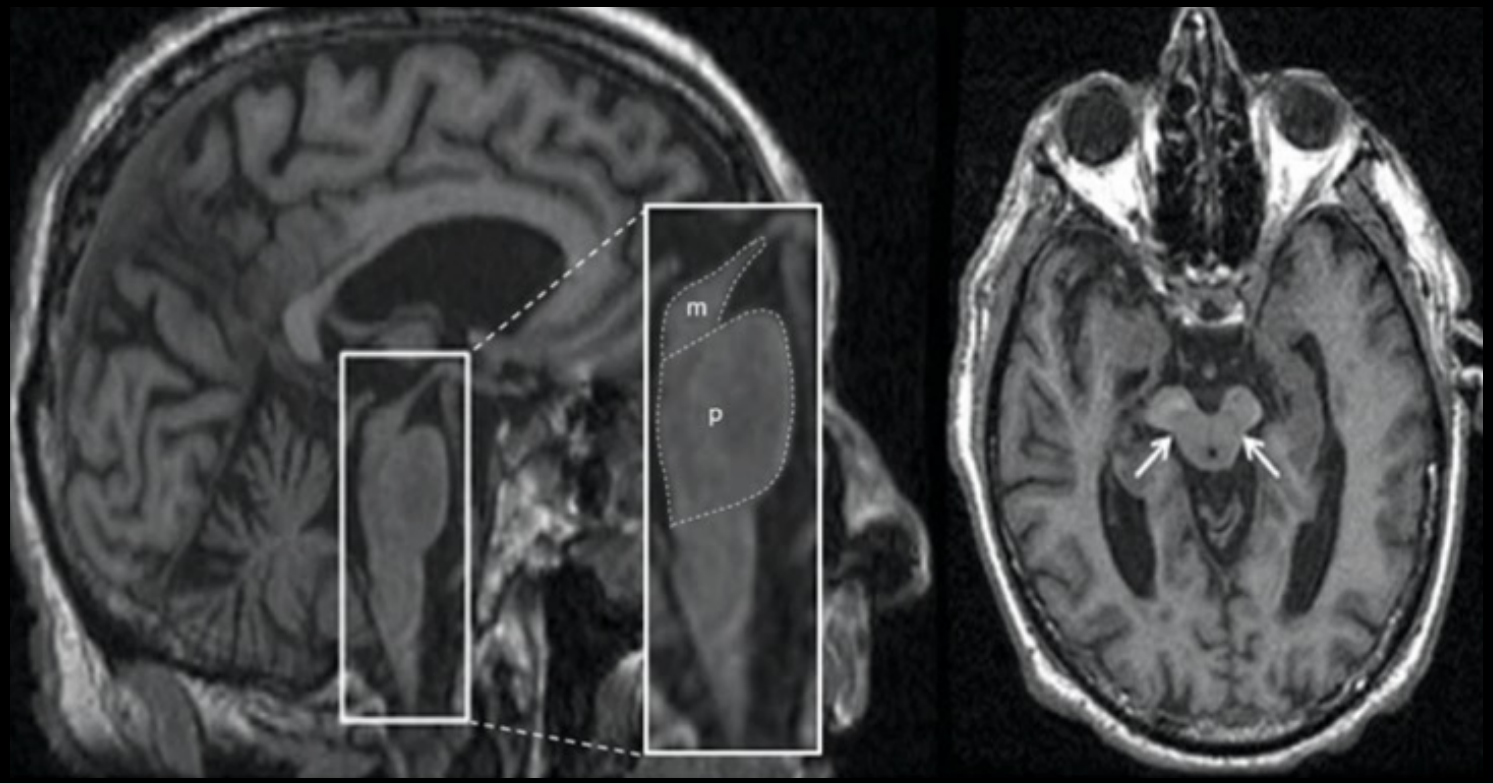
- There is a significant overlap between PSP and CBD. The main difference is that CBD patients respond to levodopa, while PSP patients do not?

Contribution of Imaging



IGURE 3 | The "swallow tail" sign. All MRI presented above are taken at the level

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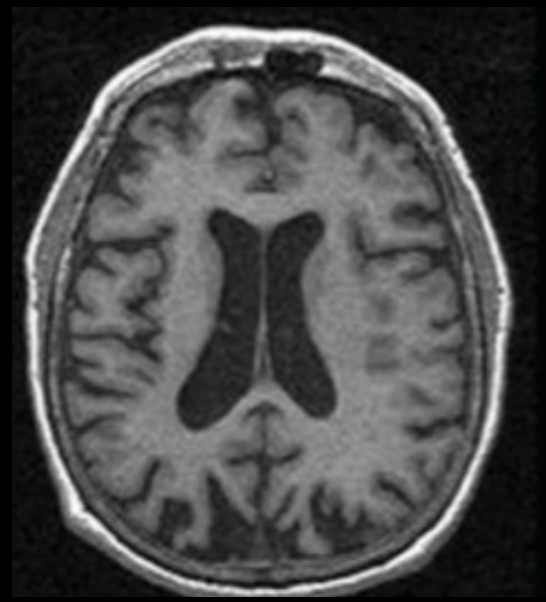

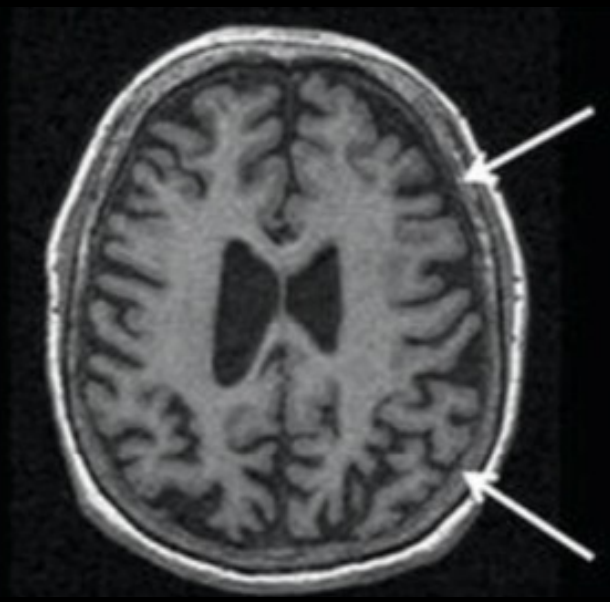

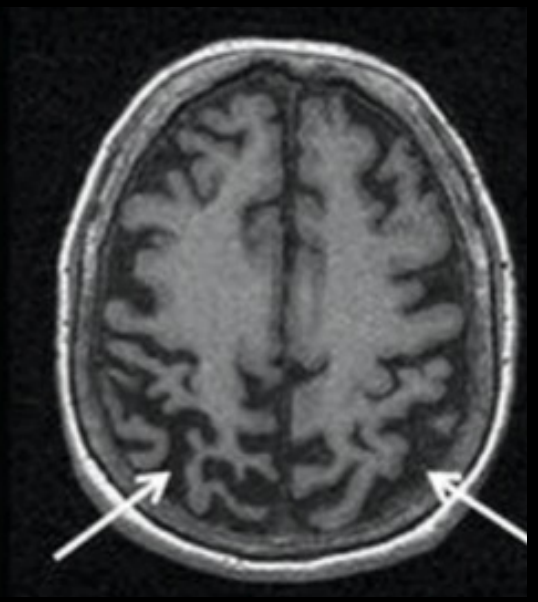

Conclusions

There is a significant overlap between Parkinson's and the Parkinson plus syndromes.

In all cases, it is important to rule out differential diagnoses such as drug-induced, vascular, encephalitis.

Clinically and pathologically, there is a significant overlap between PD, MSA and DLB, with RBD and autonomic involvement.

There is significant overlap between PSP and CBD, with multiple overlapping phenotypes, often hard to differentiate in the clinical basis. Frontal involvement, dementia, dystonia are common.