From Guidelines to Action: Movement Disorders Care Through Regional & Multidisciplinary Collaboration

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International Parkinson and Movement Disorder Society Pan American Section

In collaboration with: Baptist Health

Updates in Atypical Parkinson Syndromes

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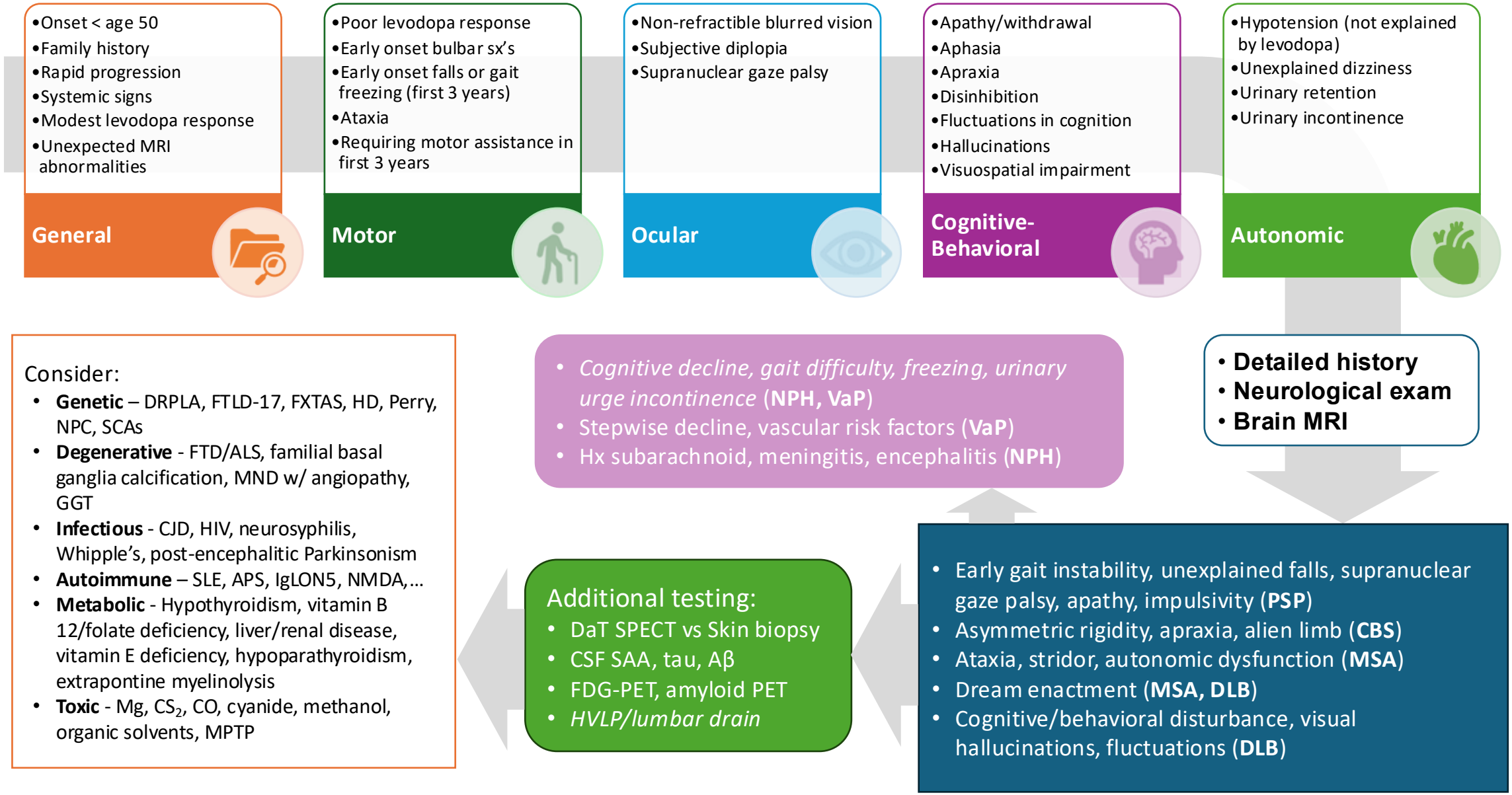
Disclosures

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- Participation in advisory boards for AbbVie, Novartis, Farrer, Deciphera/ONO Pharmaceuticals, Lundbeck; royalties from UpToDate Inc.; and travel/speaker fees for various Parkinson and movement disorders educational/CME events.

Overview, Learning Objectives



- Identify red flags and plus features for Atypical Parkinson disorders.
- Understand the diagnosis and pathological features of Atypical Parkinson disorders.
- Evaluate current treatment options and advances in therapeutics.



Bruno MK, et al. Neurology: Clinical Practice. 2024

Parkinson syndromes

- Parkinsonism . . . . . .
- PD most common, >1.2M in US alone
- Atypical parkinsonism or "Parkinson-plus" syndromes
- Clinico-pathological correlates
  - Amyloid (AD)
  - αSynuclein (PD, DLB, MSA)
  - Tau (FTD, PSP, CBD)
  - Polyglutamine
  - Prion diseases

Tremor (resting)

Rigidity

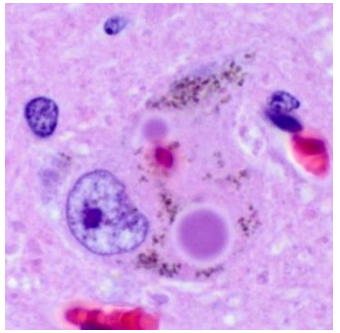
A/bradykinesia

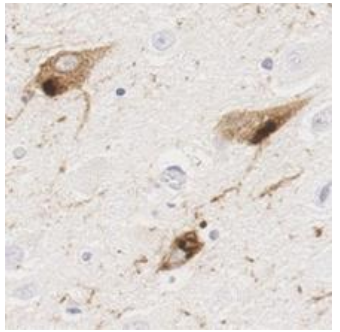
Postural instability

Flexed posture

Freezing…

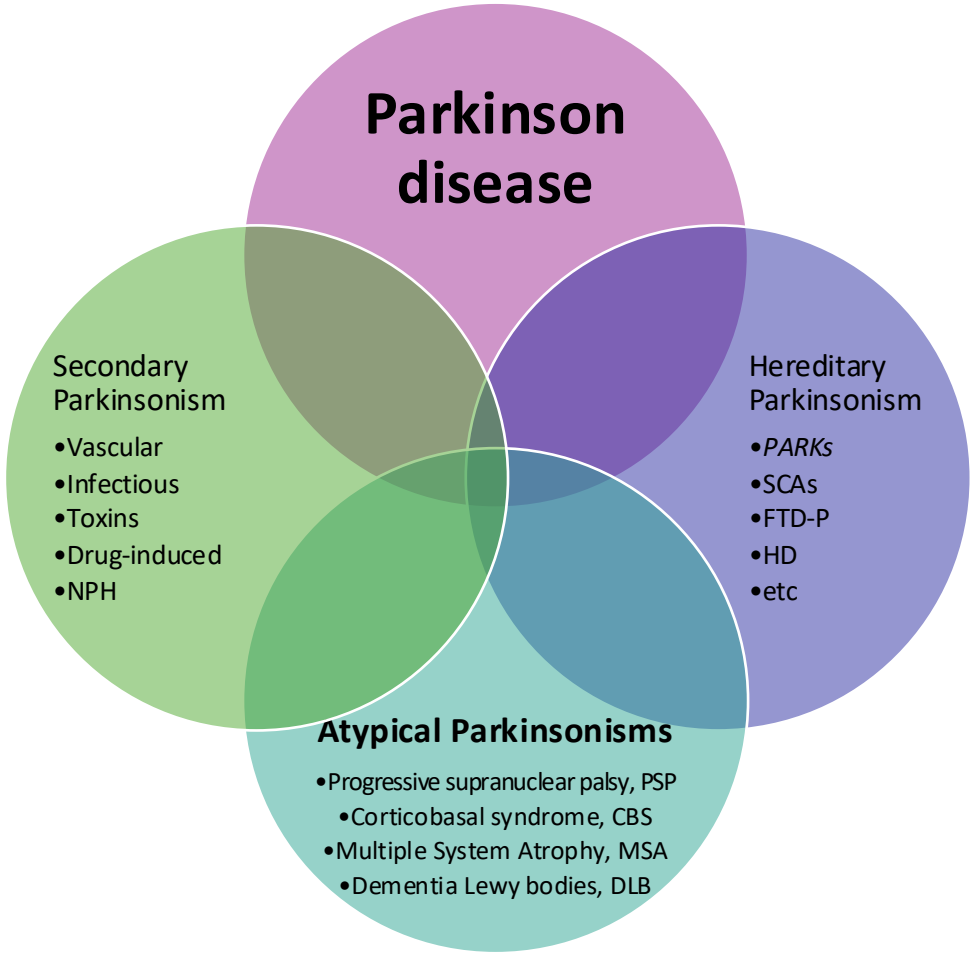


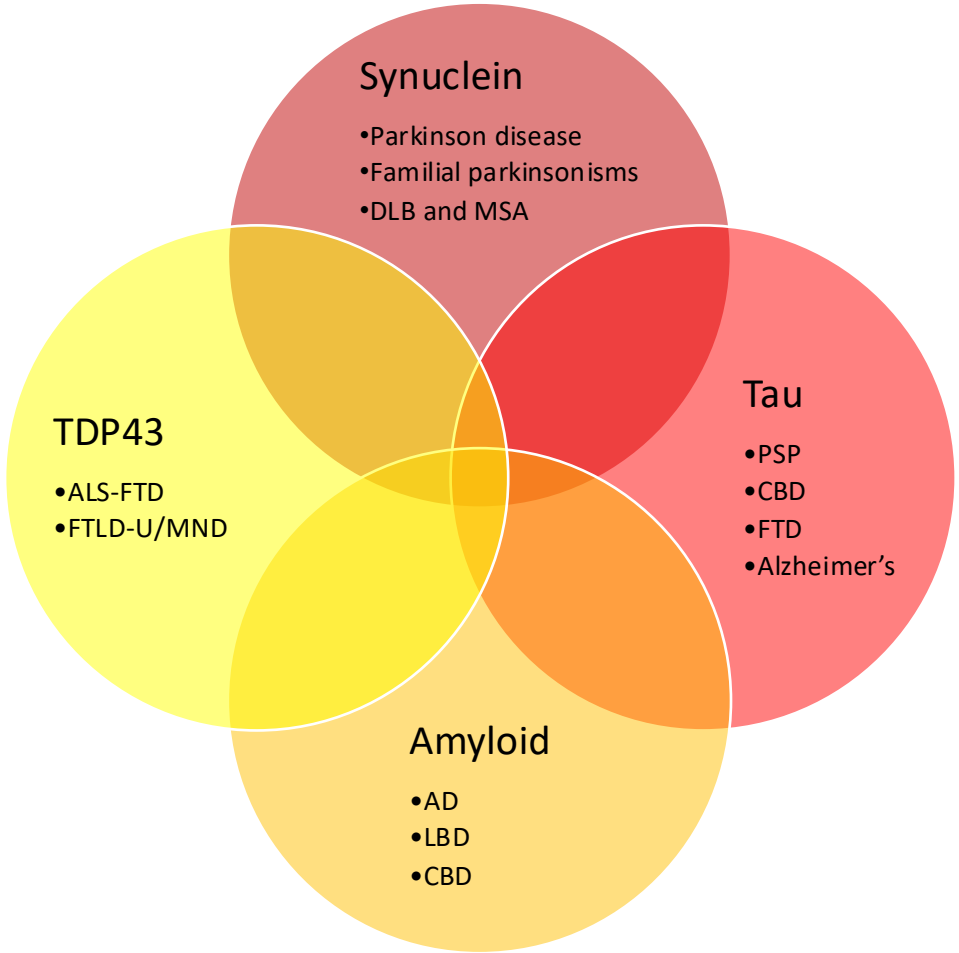




http://www.urmc.rochester.edu/neuroslides/slide199.html

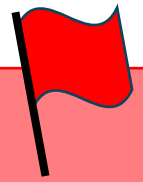
Overlap in parkinsonisms





McFarland, NR. Continuum 2016.

Is it other than PD?



Red Flags

- Rapidly, progressive disease
- Early prominent speech, swallow impairment
- Early gait difficulty, freezing, frequent falls
- Atypical tremor, pyramidal tract signs
- *Poor levodopa response (≥900 mg/day)*

PD

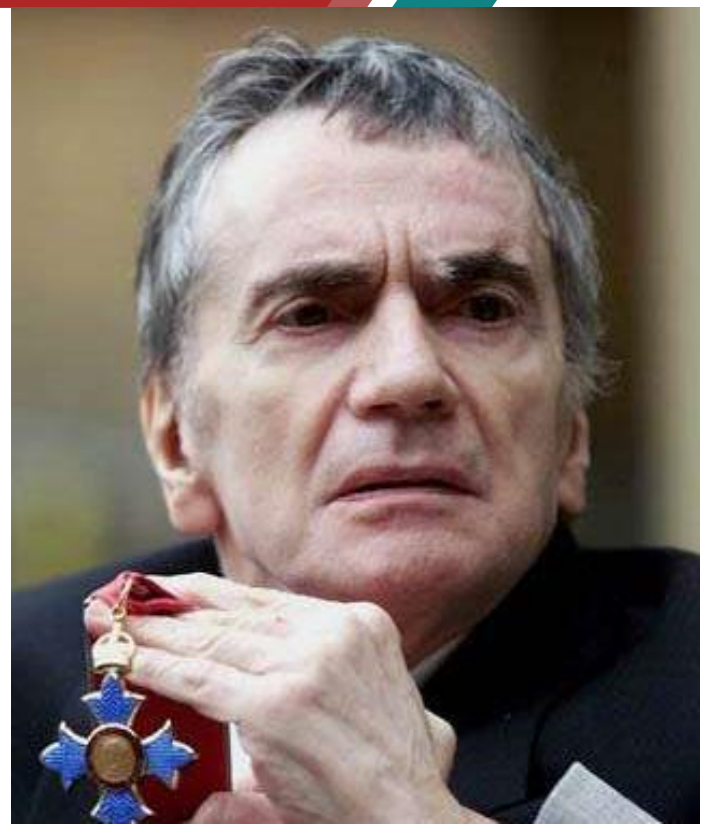
Atypical "Plus" Features

- Supranuclear gaze palsy (PSP, CBS)
- Dysautonomia, Babinski's, ataxia (MSA)
- Early cognitive impairment, dementia (DLB)
- Early behavioral, psychotic features (DLB)
- Apraxia, myoclonus, "alien-hand" (CBS)

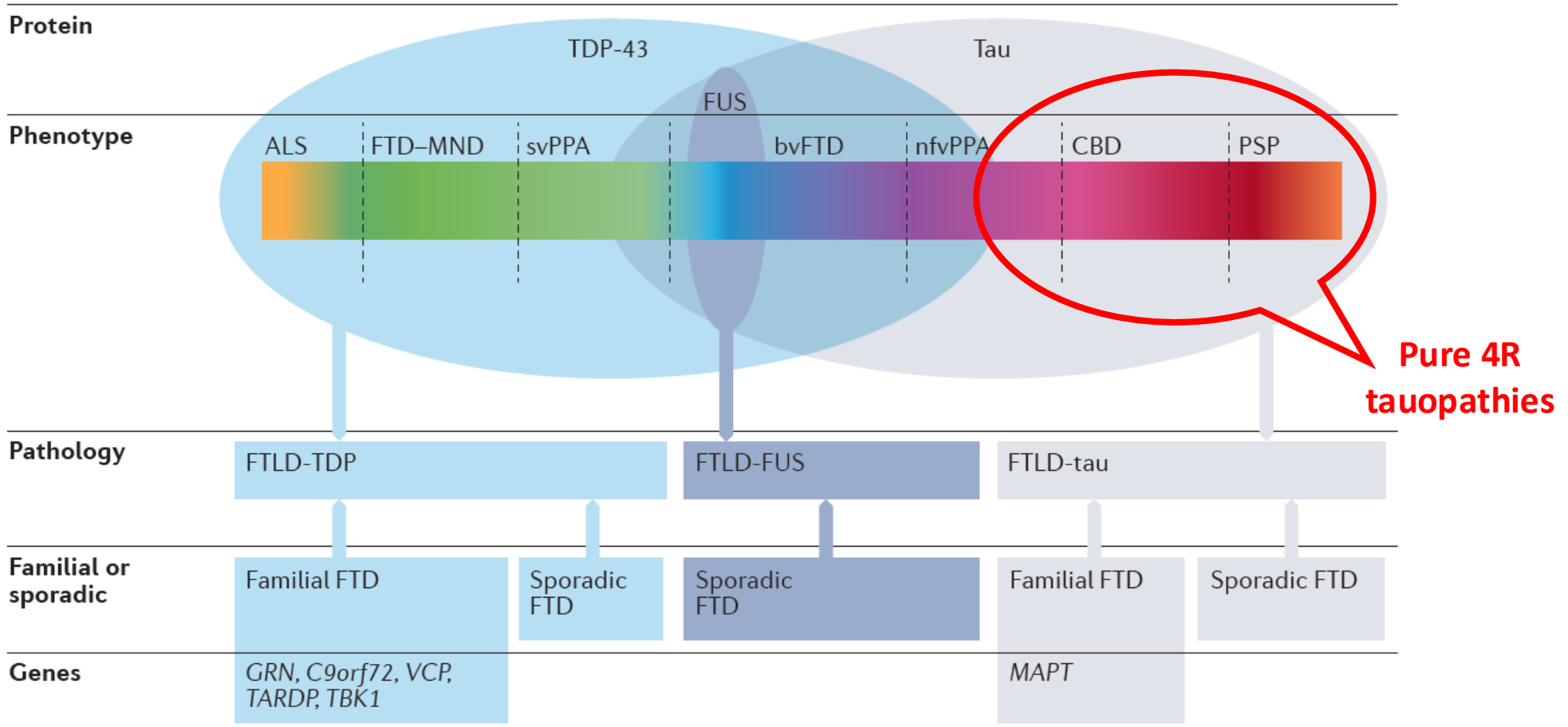
Tauopathies



- Progressive supranuclear palsy (PSP)
- Corticobasal syndrome (CBS)
- Alzheimer disease (AD)
- Chronic traumatic encephalopathy (CTE)
- Niemen Pick disease (NPD-C)
- Frontotemporal dementia (FTD-PiD or FTLD-17)



Spectrum of Frontotemporal Disorders

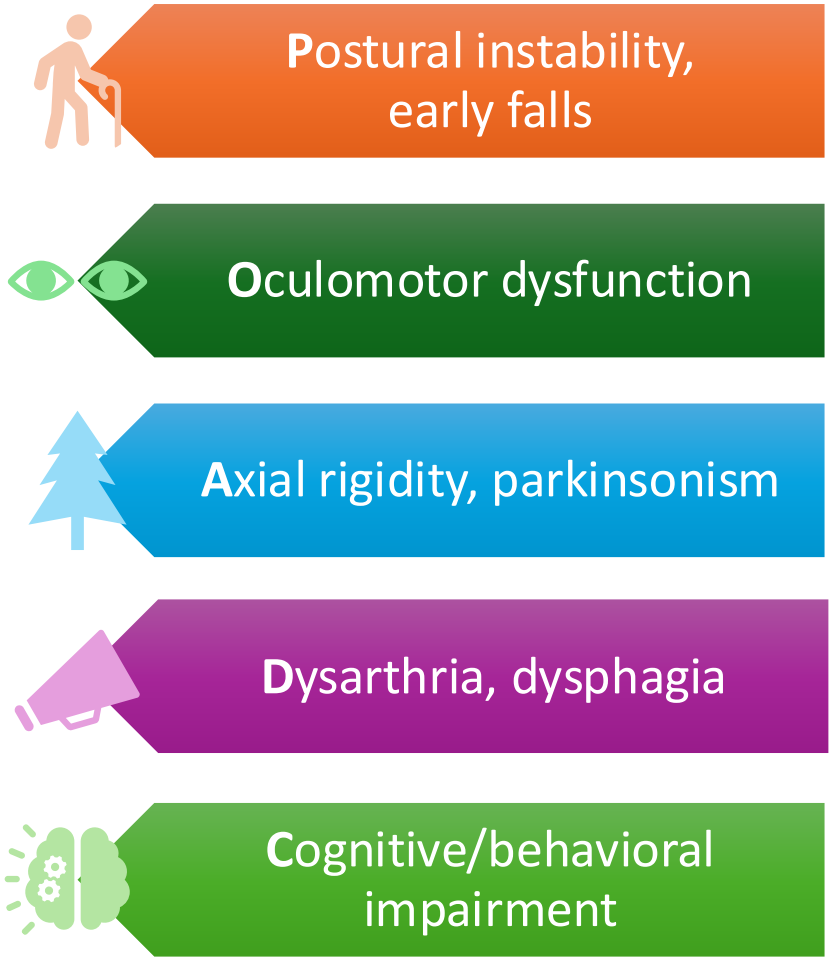


Meeter LH et al. Nat Rev Neurol 2017.

Progressive supranuclear palsy

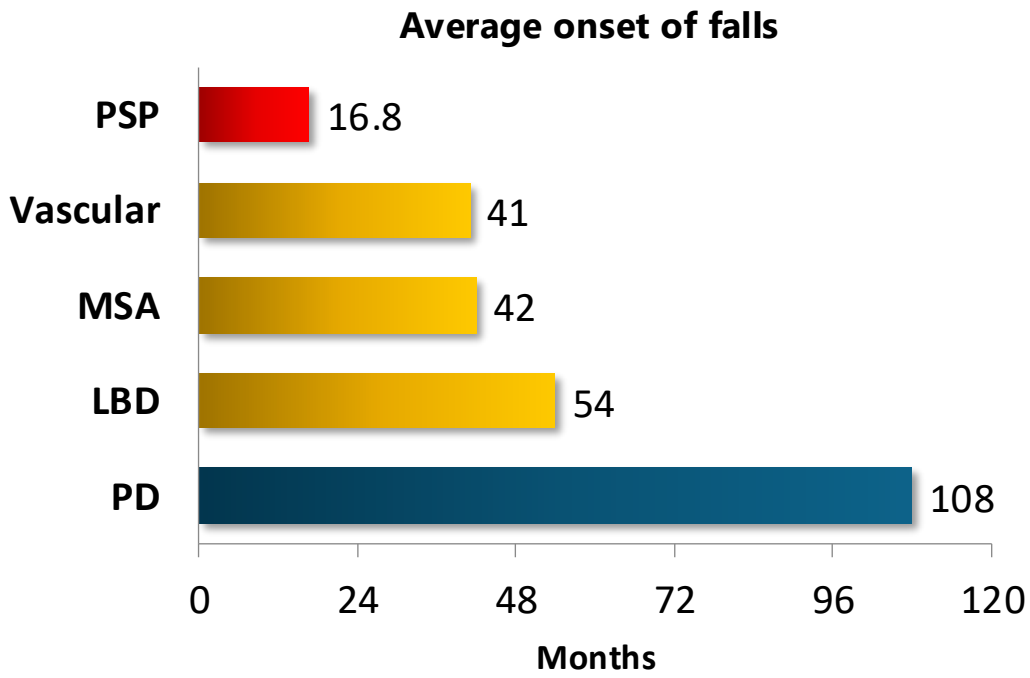
- Most common atypical parkinsonism
  - Est. prevalence 2.3 – 10.6/100,000
  - Average age of onset 63-67 (>40)
  - Estimated median survival of 6.9 yrs

Facial stare
Sloppy eating
Fragmented sleep
Urinary urgency, incontinence
Apathy, withdrawal
Anxiety, irritability
Pseudobulbar affect



PSP: Postural Instability

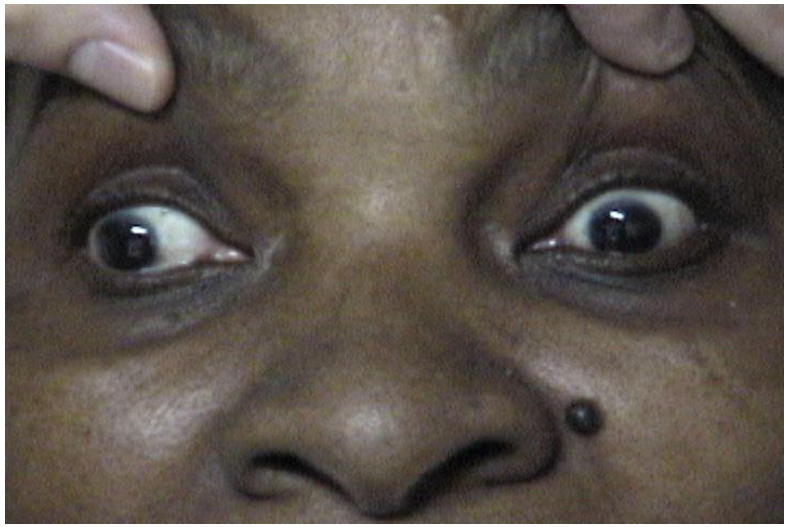
- Early onset falls, freezing < 3 years
- Falls typically backward (retropulsion)
- Gait atypical compared to PD
- Combination of factors
  - Postural instability
  - Visual-vestibular factors
  - Cognitive (impulsivity)
    - "Rocket Sign"

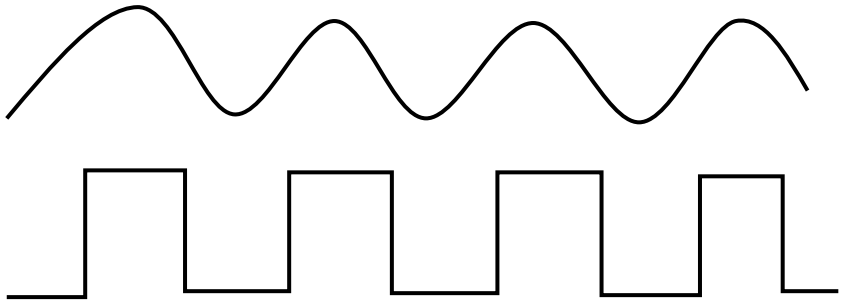


(Williams et al, 2006)

PSP: oculomotor, visual abnormalities

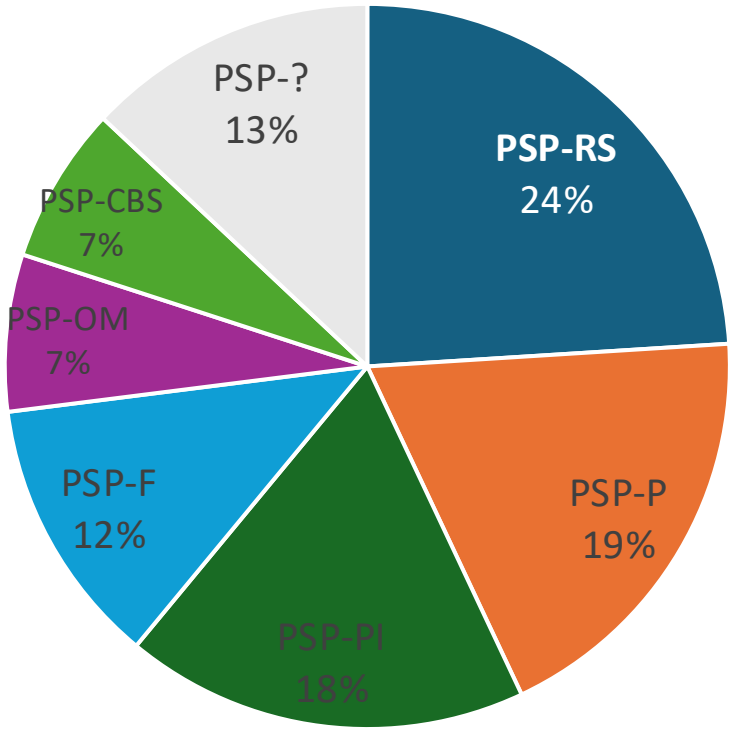
Eye complaints	Supranuclear palsy	Oculomotor abnormalities
• Blurred vision, eye discomfort, double vision, difficulty reading • Blepharospasm vs. eye lid apraxia	• Downgaze limitation > vertical • Slow horizontal saccades • Involuntary ocular fixation, “Mona Lisa” stare	• Impaired saccades • Optokinetic nystagmus • Square wave jerks





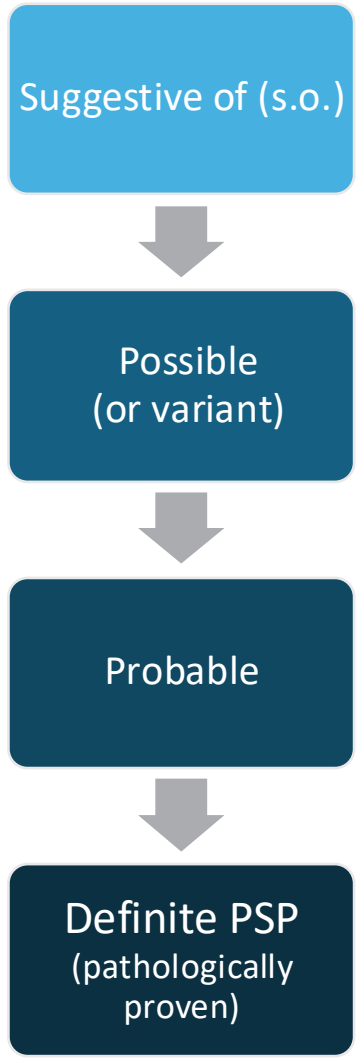
PSP Phenotypes: many faces!

Frequency PSP Phenotypes

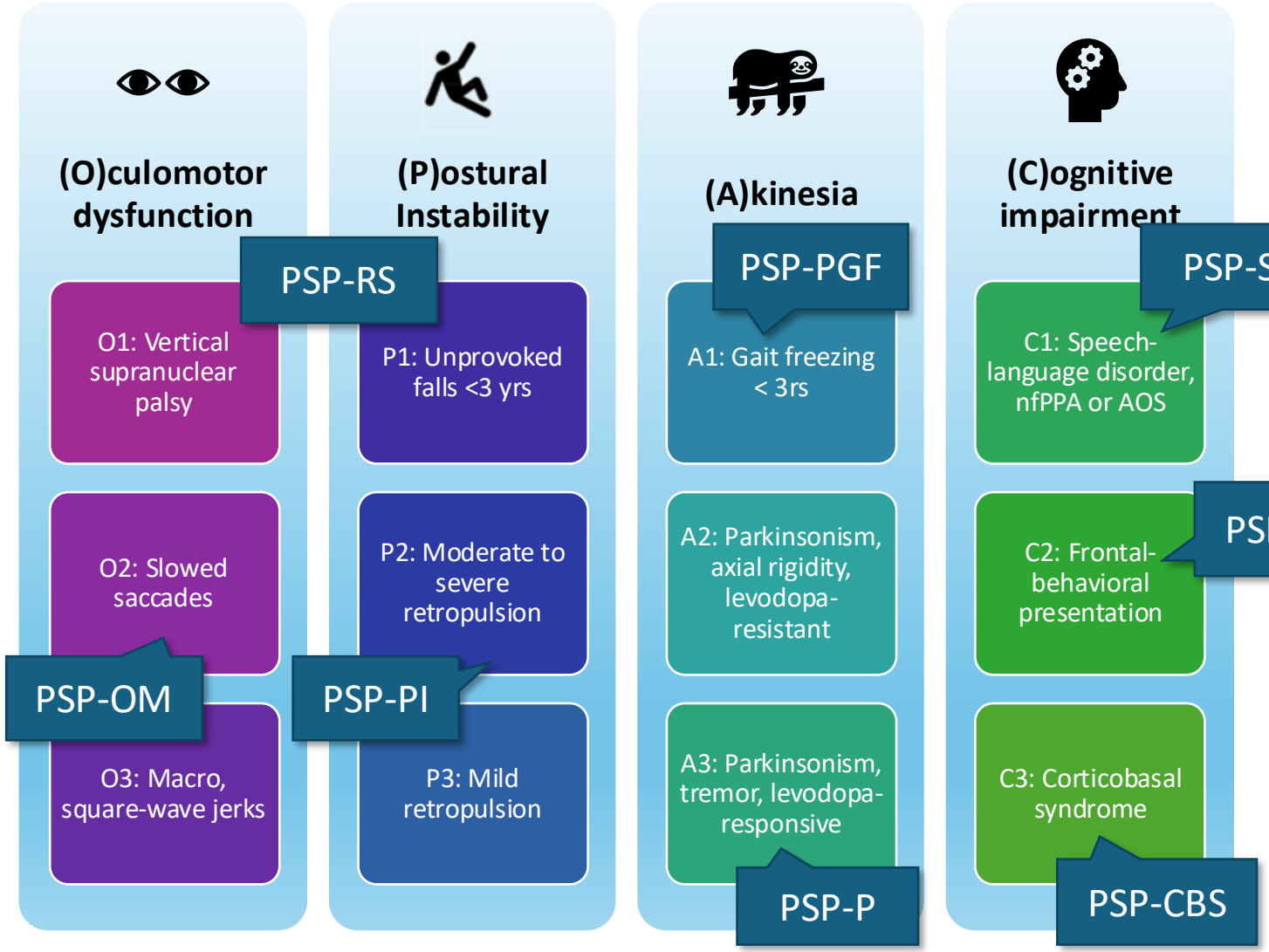


Respondek et al. Movt Dis 2014; 29:1758-1766

PSP-Richardson syndrome (RS)	
Brainstem	PSP-Oculomotor (OM)
	PSP-Postural instability (PI)
	PSP-Progressive gait freezing (PGF)
	PSP-Parkinsonism (P)
Cortical	PSP-Speech-language (SL)
	PSP-Frontal predominant (F)
	PSP-Corticobasal syndrome (CBS)
Other	PSP-Cerebellar (C)
	PSP-Primary lateral sclerosis (PLS)



Höglinger et al. MDS-PSP. 2017



Diagnosis:
ew MDS-PSP criteria

1. Sporadic disease
2. Gradual progression
3. Age ≥40 at onset of first symptom

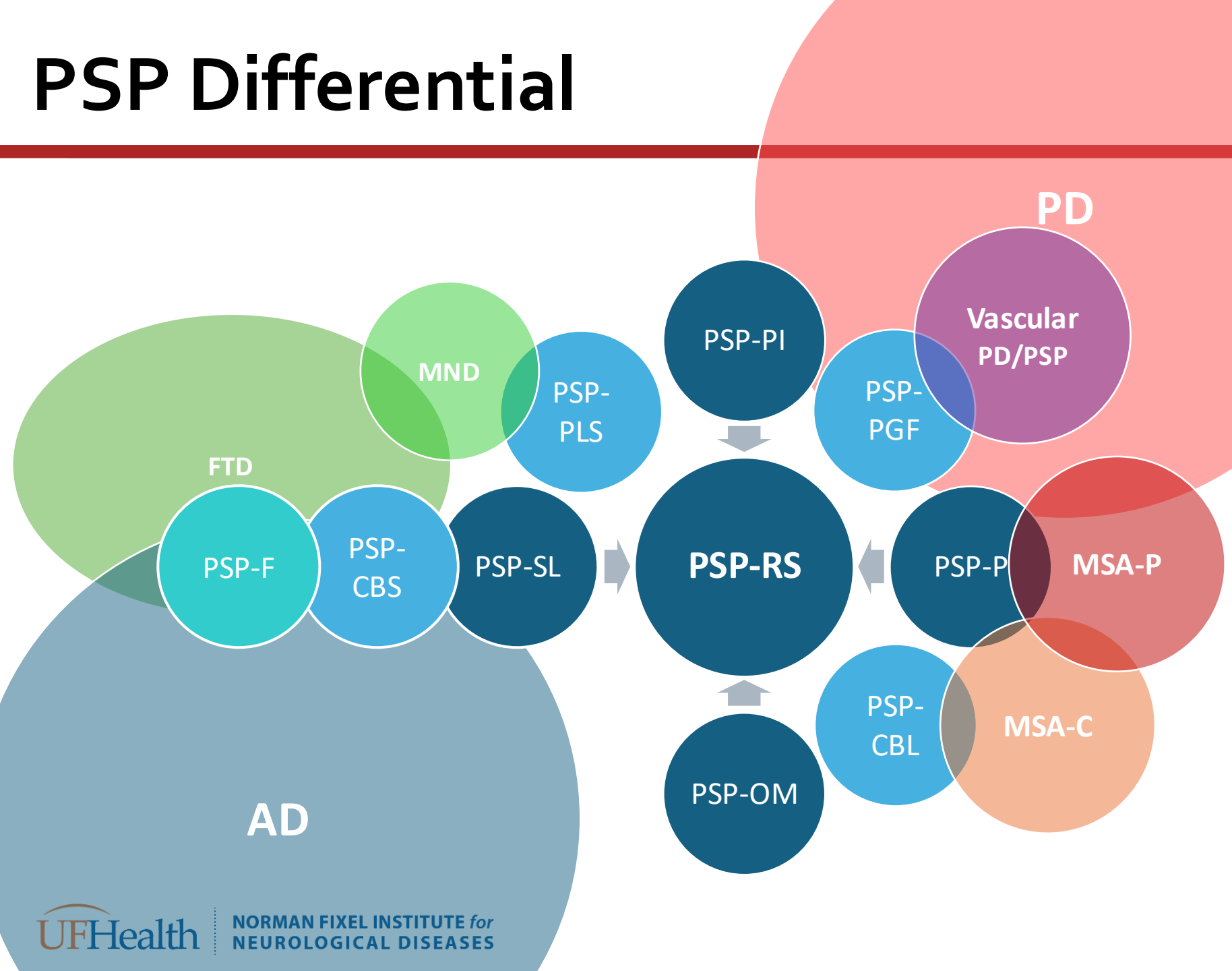
upportive data:

Clinical
CC1: Levodopa-resistance
CC2: Hypokinetic/spastic dysarthria
CC3: Dysphagia
CC4: Photophobia

Imaging
IF1: Midbrain atrophy or hypometabolism (MRI or FDG-PET)
IF2: Postsynaptic striatal dopaminergic degeneration (DAT-SPECT or F-DOPA-PET)

Höglinger et al. MDS-PSP. 2017

PSP Differential



Other PSP Mimics

NPH (normal pressure hydrocephalus)

Vascular Parkinsonism

Autoimmune

- *IgLON5* (sleep issues, bulbar sx's, up>downgaze palsy, ataxia or chorea)
- *LGI1* (FBDS, limbic)
- *DPPX* (GI, neuropsychiatric symptoms hyperexcitability)

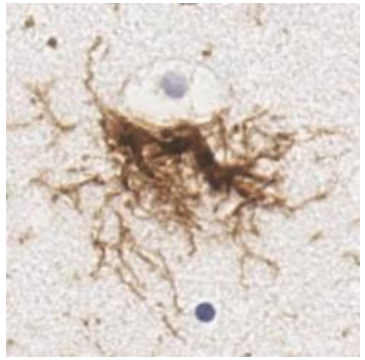
Infectious

- Whipple's (oculomasticatory myorhythmia, GI sx)
- Neurosyphilis (pupillary sx's)
- SSPE (myoclonus, encephalopathy)
- CJD (prion disease)

Genetic

- FTLD-17 *(MAPT)*
- FTLD-TDP (*C9orf72*/progranulin)
- Kufor-Rakeb *(PARK9)*
- Nieman Pick C (NPC)
- Perry Syndrome
- *POLG* (hypertrophic olivary degeneration)

PSP Pathology



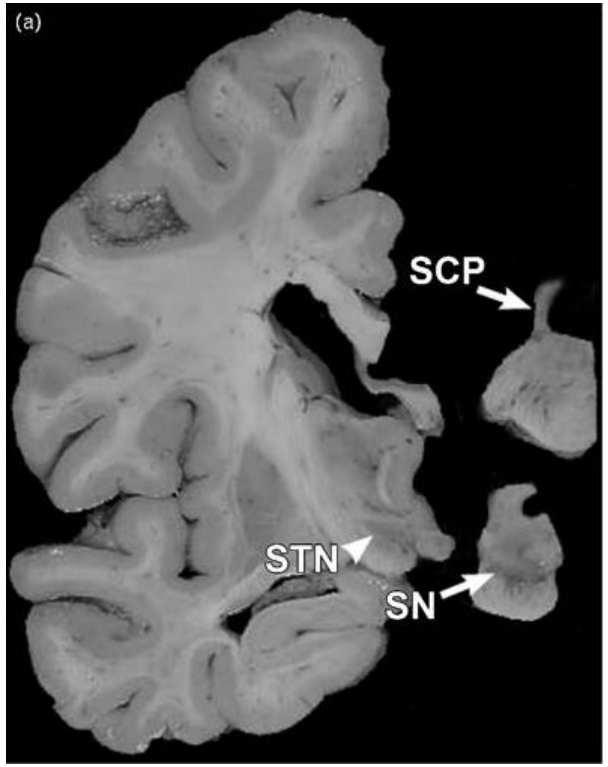
4R Tau pathology

- Tufted astrocyte
- Dentate, GP, medulla, striatum, SN, STN, pontine, oculomotor n.
- Spares cortex

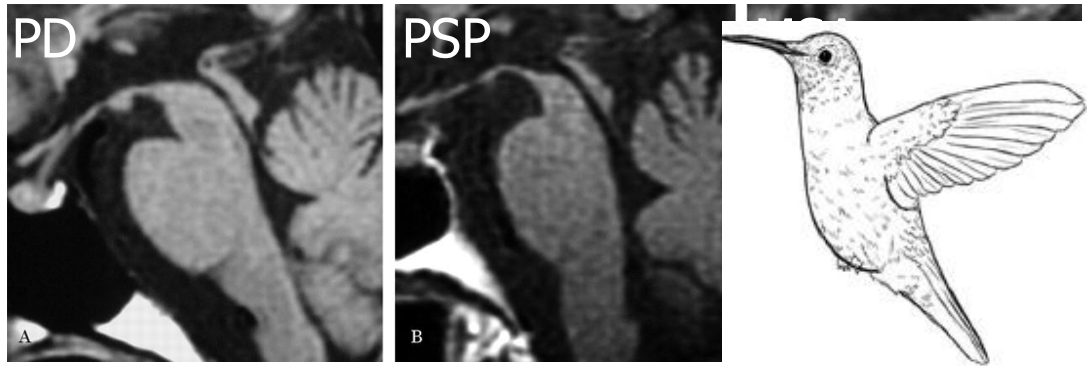
Hess, McFarland. *Seminars Neurol* 2017

Gliosis/degeneration

- Marked midbrain atrophy
- Loss pigmented cells SN
- Atrophy STN, SCP, MCP, dentate
- Mild frontal atrophy



From Dickson et al, *Curr Op Neurol* 2010

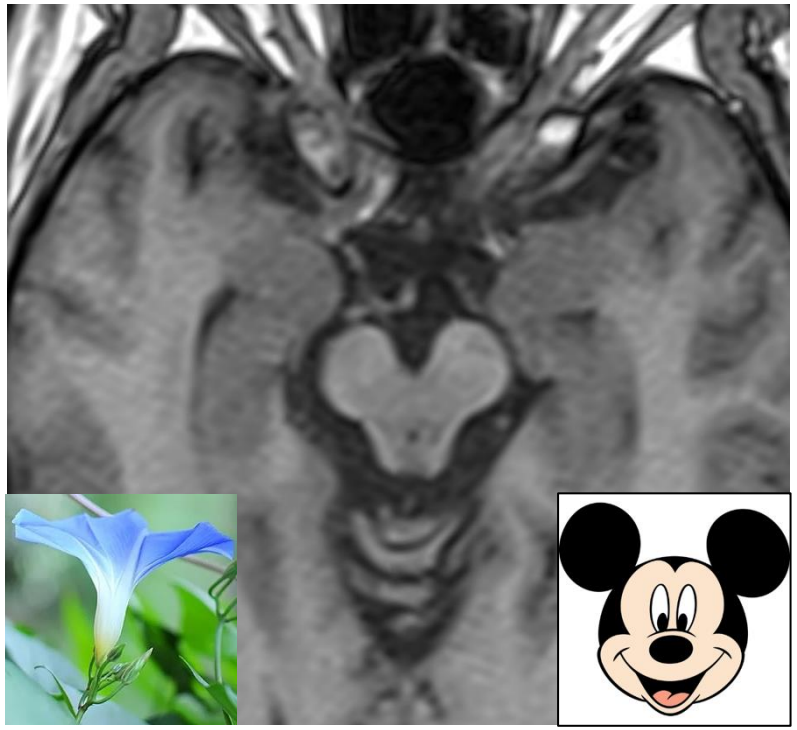


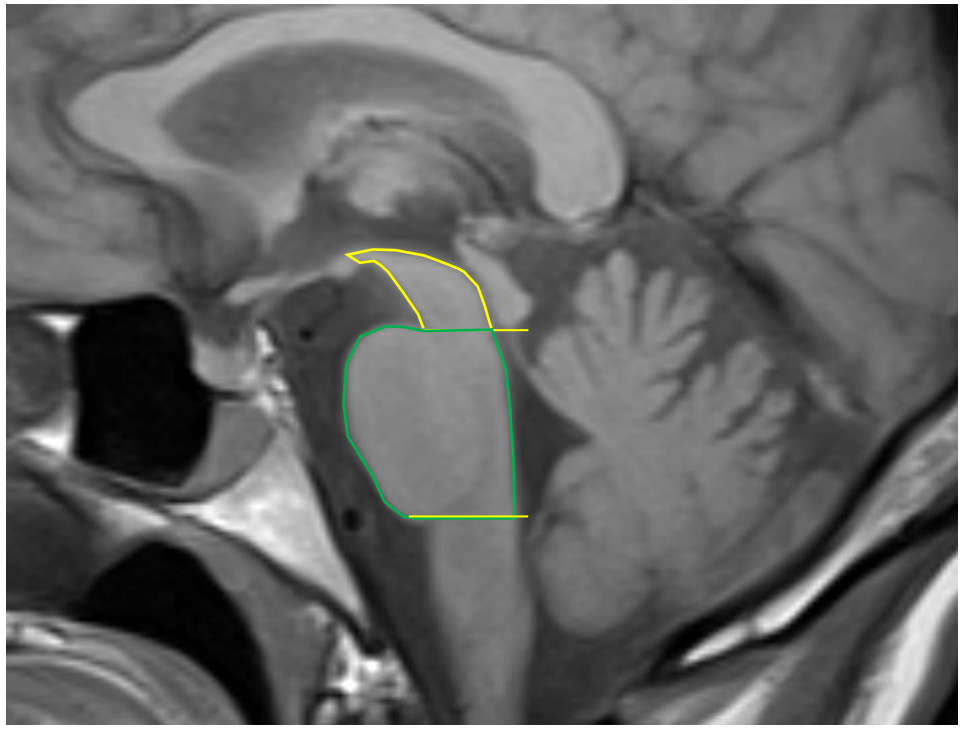
Oba, H. et al. Neurology 2005;64:2050-2055

Diagnostics

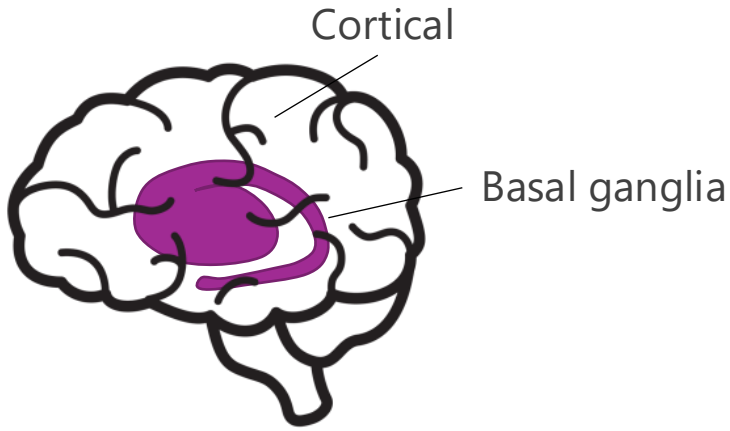
- No tissue, CSF markers
- Imaging biomarkers

MRI imaging: PSP

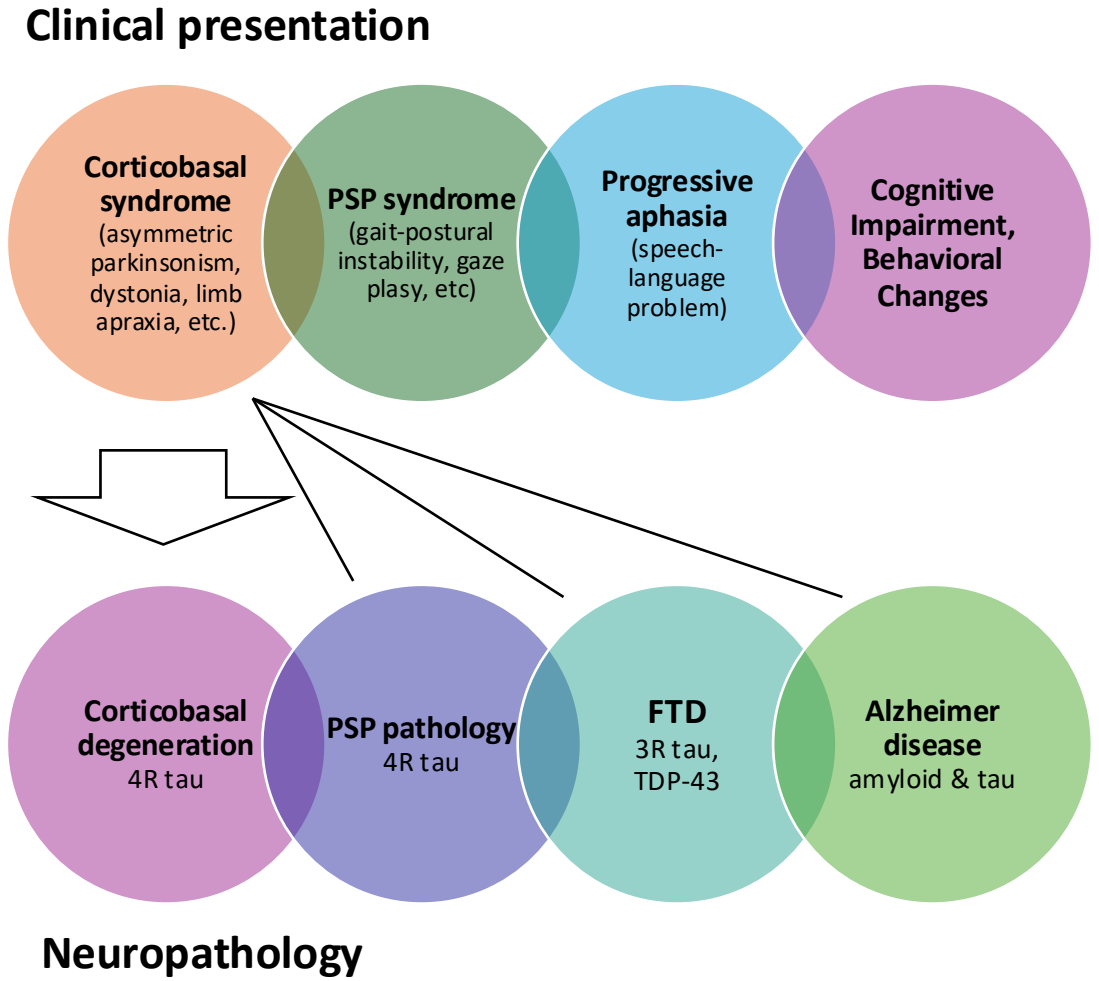




Corticobasal Syndrome

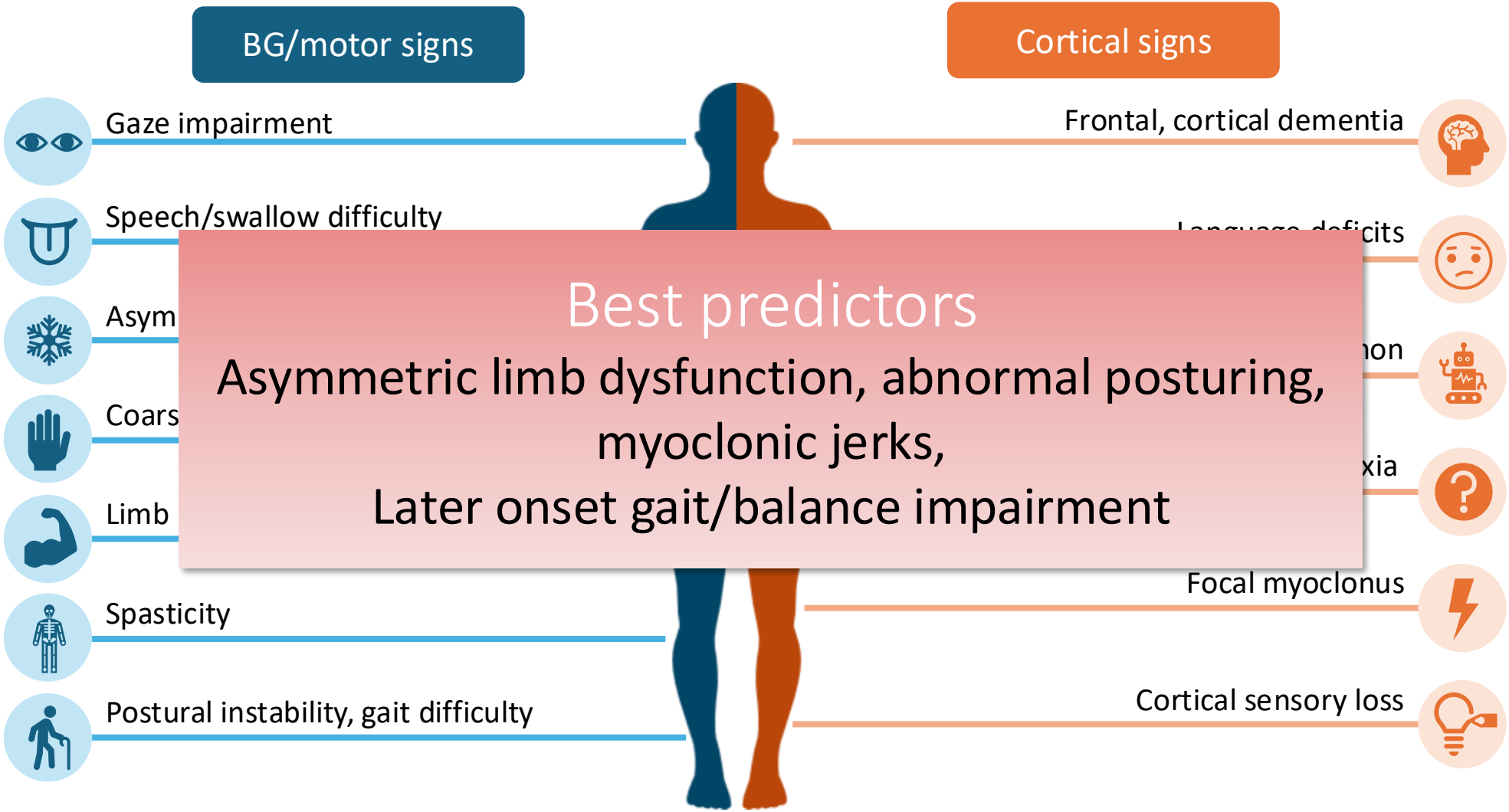


- Motor/parkinsonism, cognitive, and behavioral symptoms
- About 10x less common than PSP (incidence 0.6-0.9/100,000/yr)
- Mean onset 63±7.7 yrs (>50 y/o)
- Poor prognosis, duration 6-8 yrs



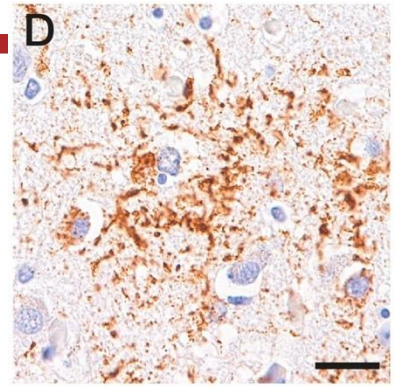
CBD features

*No ataxia
*Poor levodopa response

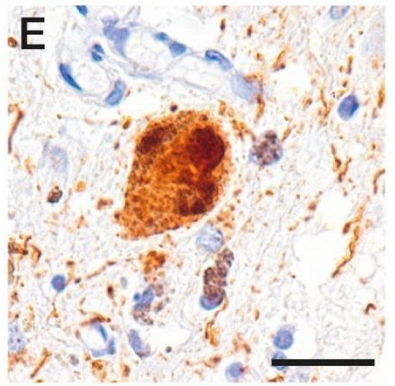


CBD pathology

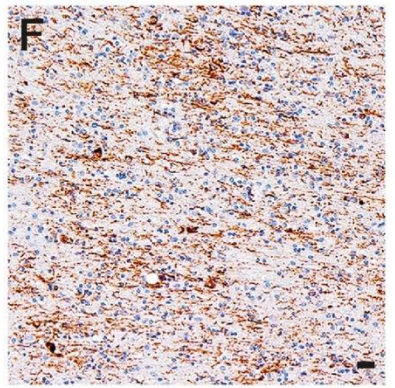
- **Typical CBD pathology is present in only ≤40% of cases**
  - Multiple other pathologies: AD, FTD, LBD, TDP-43
- CBD pathology
  - 4R hyperphosphorylated tau
  - Astrocytic plaques
  - Corticobasal inclusions
- Neuroimaging
  - CT/MRI – asymmetric frontoparietal atrophy
  - PET – asymmetric uptake



Astrocytic plaque



Neuronal corticobasal body



Threads and coiled bodies



Rosler TW et al. Prog Neurobiol 2019

PSP/CBD Treatment: medications



Parkinsonism



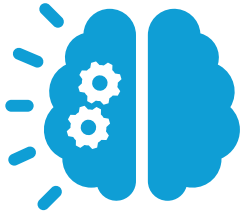
- Levodopa trial (esp, PSP-P), 200-300 mg 3 to 4 times daily
- Dopamine agonists, MAOb inhibitors – inferior to levodopa
- Amantadine – limited studies, risk of AEs

Dystonia, myoclonus



- Botulinum toxin (BoTN), muscle relaxants (avoid anticholinergics)
- Myoclonus – clonazepam, levetiracetam

Dementia



- Cholinesterase inhibitors – not recommended, may worsen motor sx's
- Memantine – no studies in PSP/CBS

Mood, emotions



- Apathy – "activating" SSRI/SNRI's, bupropion, amanatadine
- Depression/anxiety - SSRI, SNRI preferred over tricyclics
- PBA: dextromethorphan-quinidine

Other



- Urinary frequency – antispasmodics (eg, solifenacin), mirabegron (β3AR), BoNT
- Retention – tamsulosin (α1A), pyridostigmine, int. self catheterization
- Insomnia – melatonin, trazodone, zolpidem

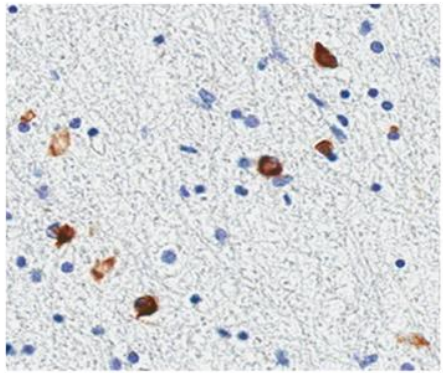
The Synucleinopathies



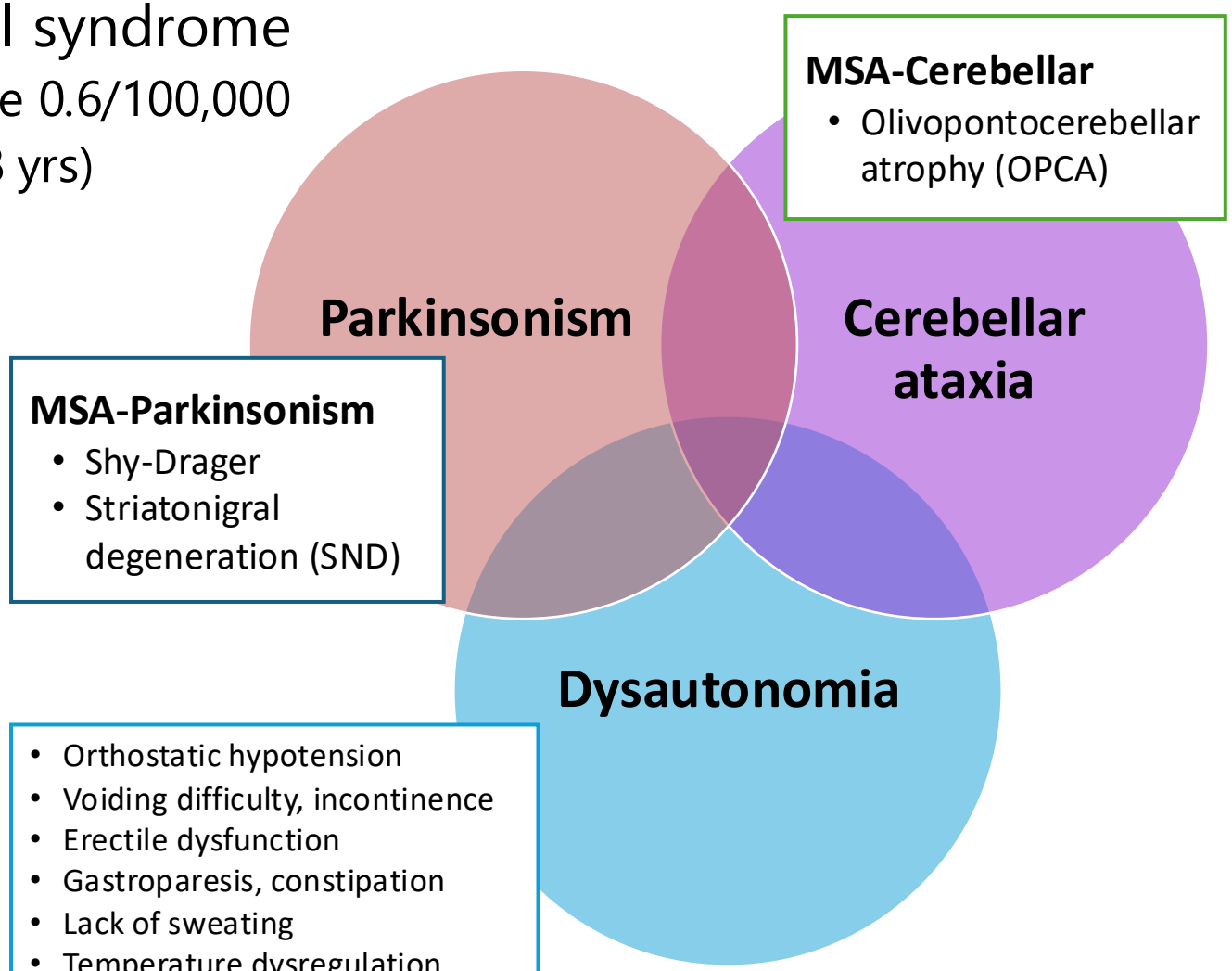
- Multiple System Atrophy (MSA)
- Dementia with Lewy bodies (DLB)
- Parkinson disease with dementia (LBD/PDD)

Multiple System Atrophy

- Second most common atypical syndrome
  - Prevalence ~3/100,000; incidence 0.6/100,000
  - Sporadic adult onset (median 58 yrs)
  - Rapid progression, disability
- Many faces, same disease

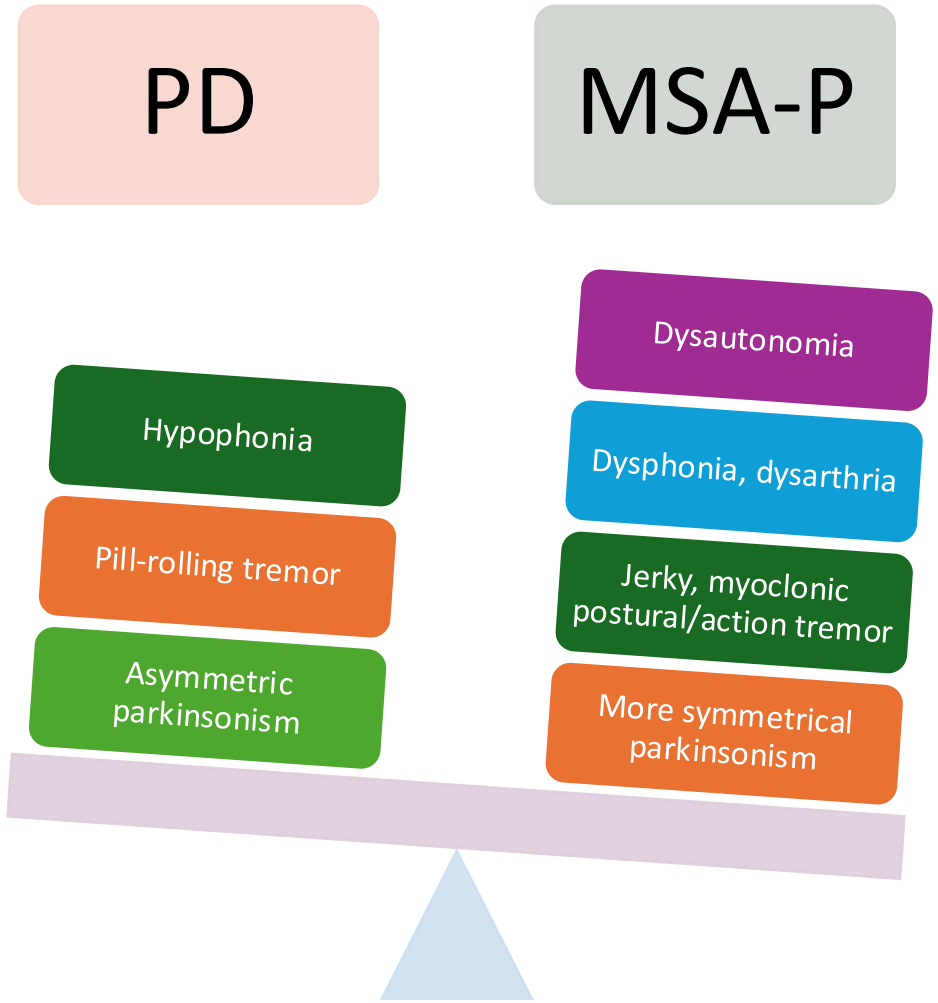


Lewy body pathology +
Glial cytoplasmic inclusions (GCI)



MSA-Parkinsonism vs PD

- **Features (red flags)**
- *Rapidly progressive parkinsonism*
- Poor, non-sustained levodopa response
  - Facial dyskinesias, dystonia, confusion
- Early speech / swallow difficulty
- Atypical, jerky tremor
- Unexplained pyramidal signs (Babinski's)
- Sleep disordered breathing (OSA)
- Inspiratory stridor
- Postural deformity (dropped head, flexion or tilt at waist [camptocormia, Pisa])
- Early gait difficulty, falls
- *Dysautonomia (69% vs 5% in PD)*



MSA-Cerebellar (OPCA)

- Variable Onset
- Sporadic vs familial MSA-C
- Overlap with genetic forms of ataxia with parkinsonism
  - Spinocerebellar ataxias (SCA's)
  - DRPLA
  - Friedrich's ataxia

Cerebellar features
- Gait or limb ataxia
- Cerebellar dysarthria
- Ocular ataxia, nystagmus



Additional motor
- Hyperreflexia
- Weakness/atrophy
- Parkinsonism, 8.2%



Dysautonomia
- Urinary retention
- urge incontinence
- Early ED
- Neurogenic OH

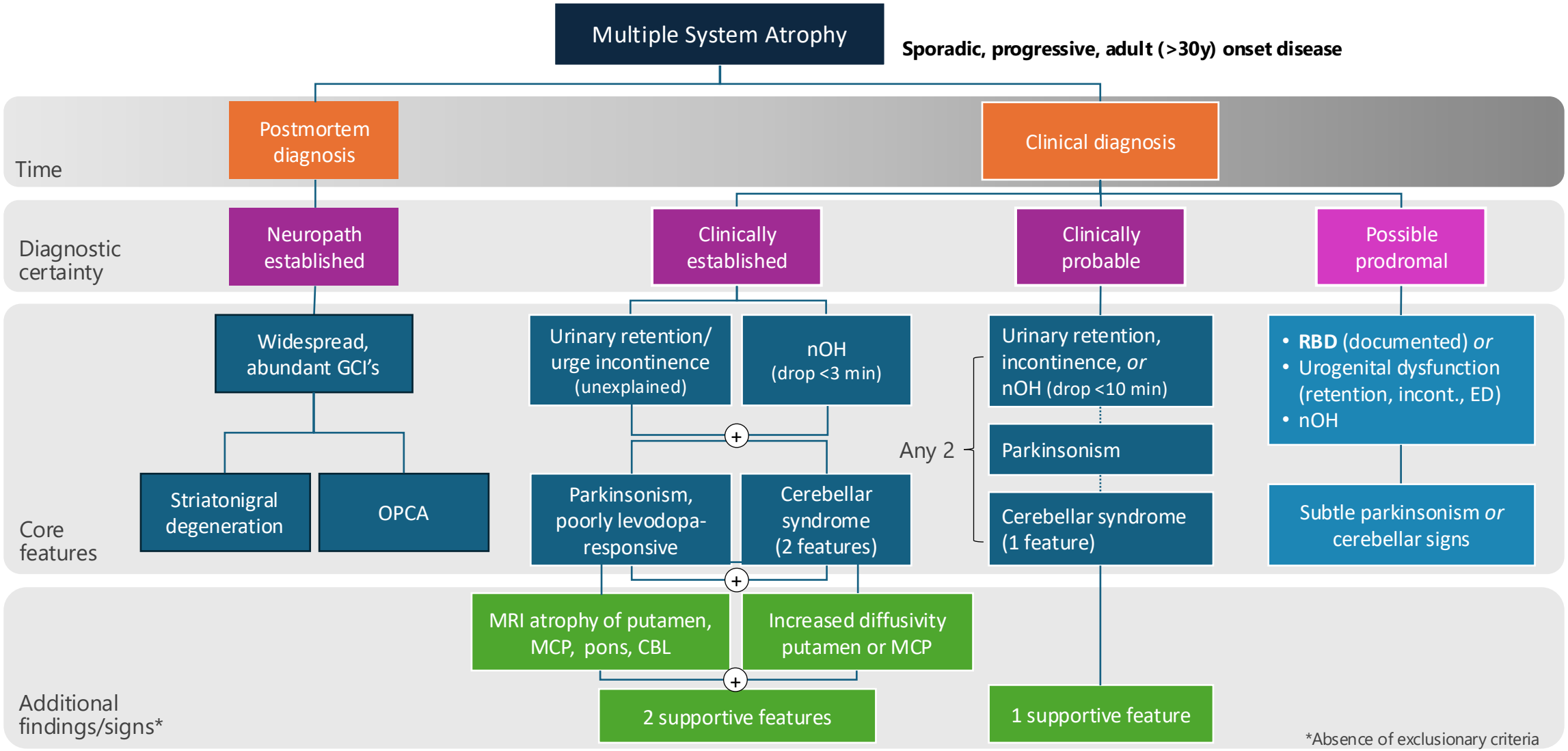


Mood
- Depression, anxiety
- Emotional lability
- Pseudobulbar affect (PBA)



Progressive dementia
- Visuospatial-executive, rarely memory (short-term)





Supportive features

Within 3 yrs motor onset:
- Rapid progression
- Severe impairment speech or swallow
- Moderate-severe postural instability

- Jerky myoclonic tremor
- Unexplained Babinski
- Craniocervical dystonia (LID)
- Postural deformity

- Stridor, inspiratory sighs
- Cold discolored hands/feet
- ED (< age 60)
- Pathological crying or laughter

UFHealth | NORMAN FIXEL INSTITUTE for NEUROLOGICAL DISEASES

Wenning G, et al. *Mov Disord* 2022

MSA neurodiagnostics



Autonomic testing

- Orthostatics, tilt-table, valsalva
- Thermoregulatory sweat test, QSART
- Neurogenic bladder, sphincter EMG
- Gastric emptying study, anorectal manometry



Sleep study

- Quality
- Sleep apnea (CPAP)
- Stridor
- REM sleep behavior (RBD)
- RLS/RLMS

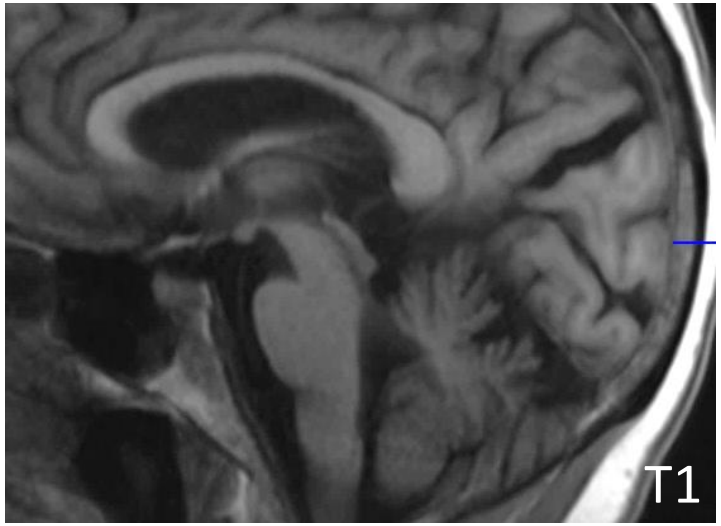


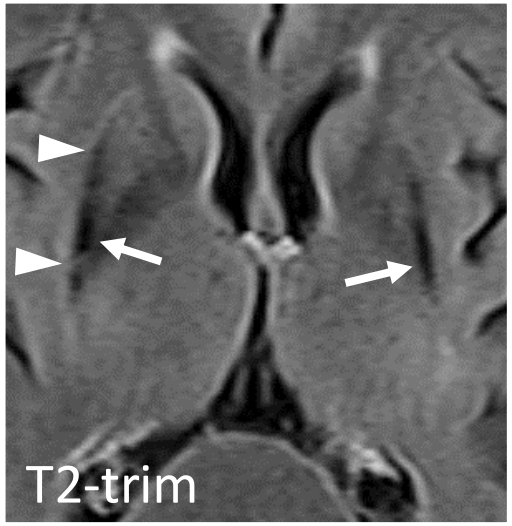
Neuroimaging: MRI

- T2 hypointensity posterolat. putamen
- Slit hyperintensity lateral putamen (89% MSA-P)
- Abnormal DWI signal CBL peduncles (MSA-C)
- “Hot cross bun” sign (63%), pontine atrophy

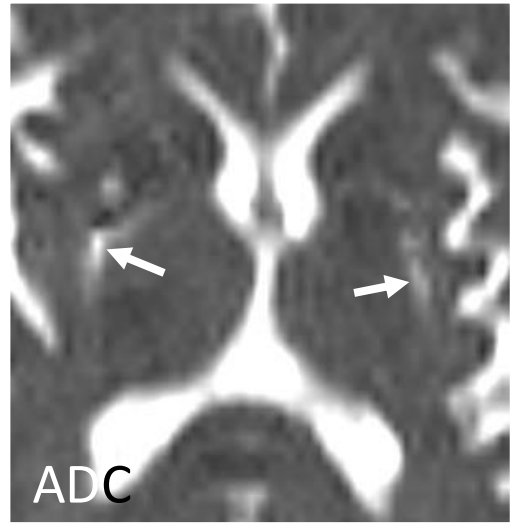
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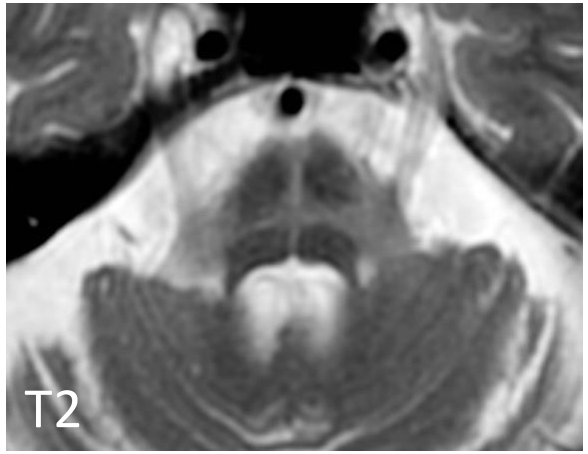
MSA Imaging



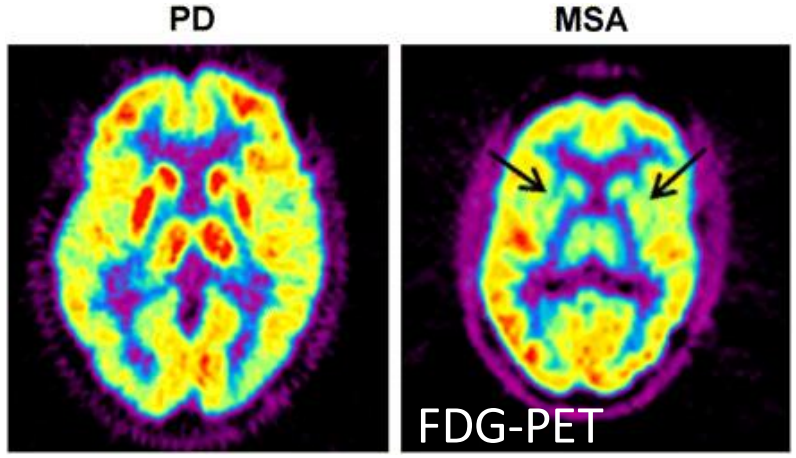








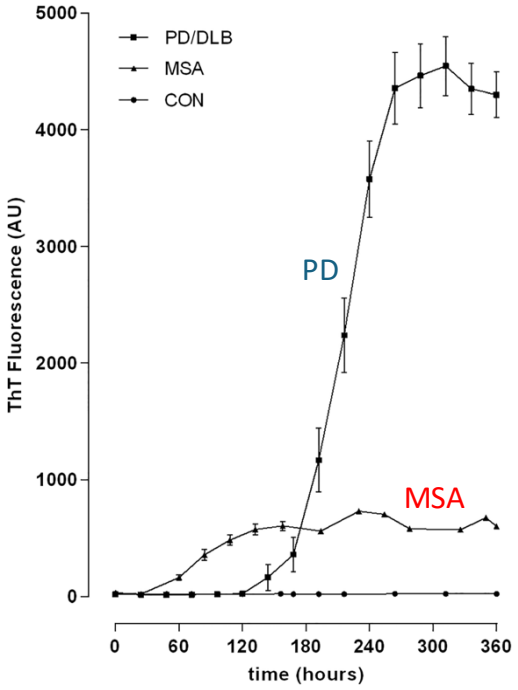




Brooks D. J Nuc Med 2010.

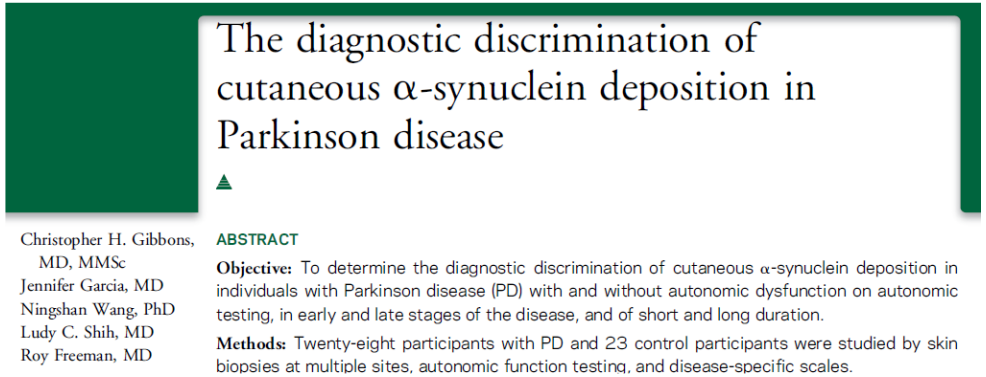
Fluid and tissue biomarkers

- α-synuclein(Syn) & neurofilament light chain (NfL)
  - CSF & plasma inconsistently increased
  - Seeding aggregation assays, SAA (RT-QuIC, PMCA)
- Syn-One (CND Lifesciences)
  - Skin biopsy x3
  - pSyn IHC



	Sensitivity	Specificity
PD	92.3	>96
MSA	98.2	>96
DLB	96.0	>86
PAF	100	>96

Gibbons C, et al. *Neurology* 100 (15), 2023.



The diagnostic discrimination of cutaneous α-synuclein deposition in Parkinson disease

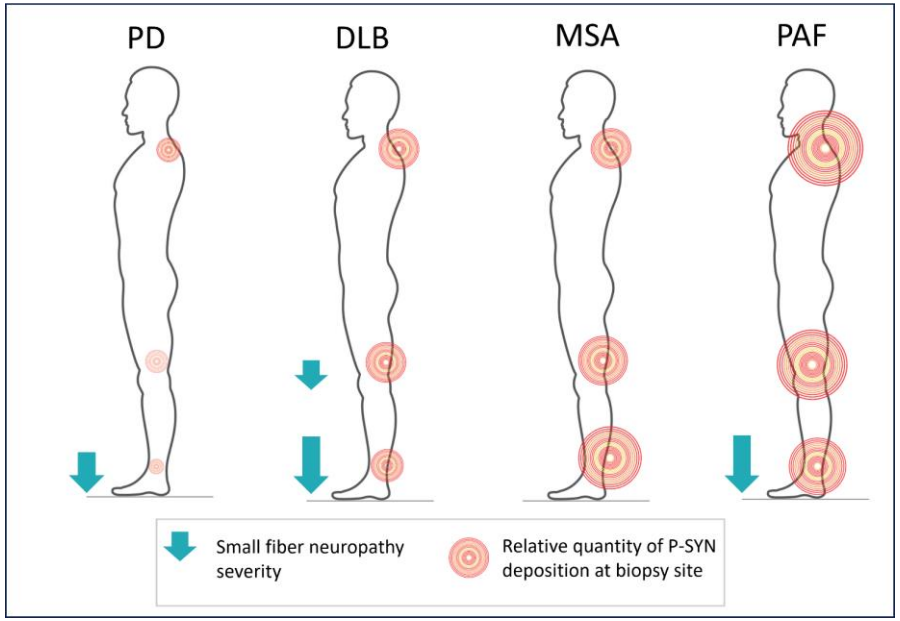
Christopher H. Gibbons, MD, MMSc
Jennifer Garcia, MD
Ningshan Wang, PhD
Ludy C. Shih, MD
Roy Freeman, MD

ABSTRACT

Objective: To determine the diagnostic discrimination of cutaneous α-synuclein deposition in individuals with Parkinson disease (PD) with and without autonomic dysfunction on autonomic testing, in early and late stages of the disease, and of short and long duration.

Methods: Twenty-eight participants with PD and 23 control participants were studied by skin biopsies at multiple sites, autonomic function testing, and disease-specific scales.

Neurology® 2016;87:505–512



CND LifeSciences

MSA treatment

Multi/interdisciplinary

Neurology

Cardiology

Gastroenterology

Urology

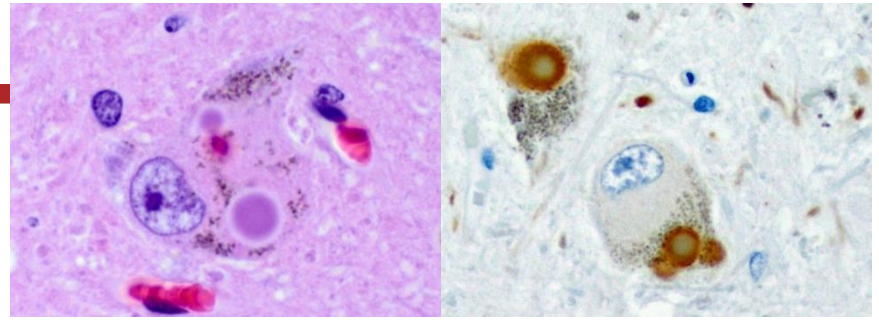
Sleep/pulmonary

Psychiatry

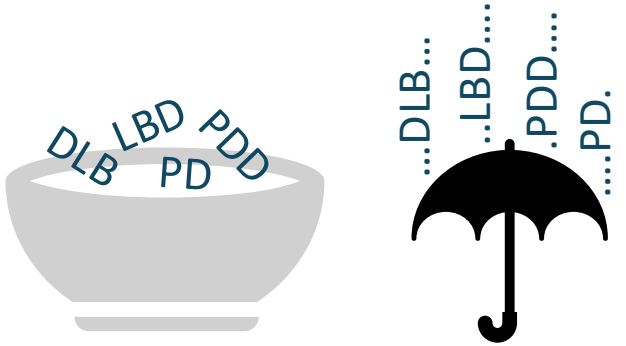
Palliative, etc.



Parkinsonism-dementia



- Cognitive impairment/dementia common in parkinsonisms
  - Prevalence of MCI in PD ranges 25-65%
  - Mean prevalence dementia in PD ~30% (up to 75-80% develop signs)
  - Overlap with other syndromes: DLB, AD, FTLD, atypical Parkinsonisms
- Lewy body dementia
  - 2nd most common neurodegenerative dementia
  - Umbrella term for both DLB and PDD
  - DLB vs PDD? (one year rule, but continuum)





VIEWS & REVIEWS

Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

McKeith IG, et al. *Neurology®* 2017;89:88-100

Predictors *Less likely*

- Presence of CVD, focal signs
- Other physical or brain disease sufficient to explain symptoms
- Parkinsonism as core feature or appears only w/ severe dementia

Diagnosis Dementia + core features

- **Probable**: 2 or more core, or 1 core+1 or more indicative biomarkers
- **Possible**: 1 core, or 1 or more indicative biomarkers
- "One-year rule" for DLB vs PDD

Essential

Dementia:
progressive cognitive decline, esp. attention, visuospatial, executive (no prominent memory impairment)

Interferes w/ normal social, occupation or ADLs

***Core**

Fluctuating cognition, attention or alertness

Recurrent visual hallucinations, well formed, detailed

REM sleep behavior (may precede dementia)

Parkinson motor features

Supportive

Neuroleptic sensitivity

Postural instability, falls

Syncope, unresponsive episodes

Severe autonomic dysfunction

Hypersomnia

Hyposmia

Hallucinations, delusions

Apathy, anxiety, or depression

Ind.Biomarker

Reduced dopamine transporter uptake in BG by SPECT or PET.

Abnormal (low) 123 iodine-MIBG myocardial scintigraphy.

Polysomnography confirmation of REM sleep without atonia.

Sup.Biomarker

CT/MRI:
Relative preservation of medial temporal lobe structures

SPECT/PET:
Generalized low uptake with reduced occipital activity (cingulate island sign) on FDG-PET.

Quantitative EEG:
Prominent posterior slow-wave activity with periodic fluctuations in pre-alpha/theta range.

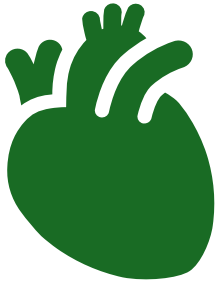
DLB/PDD therapy

Parkinsonism



- Levodopa useful, but can exacerbate hallucinations
- Dopamine agonists, non-DA agents generally avoided

Autonomic



- OH – behavioral changes, medications (midodrine, fludrocortisone)
- Urinary frequency/urgency
  – antispasmodics,
  – mirabegron or vibegron
  – desmopressin

Cognitive decline



- Cholinesterase inhibitors – rivastigmine, donepezil
- Memantine – monotherapy vs combined (no evidence)

Fluctuations, RBD



- Evaluate metabolic, infectious causes
- Supportive care
- RBD: melatonin, clonazepam (benzo's otherwise contraindicated)

Psychosis



- Quetiapine, clozapine (proven benefit Klein et al, 2003)
- Pimavanserin – 5-HT2A inverse agonist, delayed action

Supportive care

- It takes a Village!
- Multidisciplinary care



Physical therapy

- Mobility
- Fall prevention

Occupational therapy

- Maintain independence
- Activities of daily living



Speech Pathology

- Speech impairment
- Swallow: prevent choking, aspiration

Nursing

- Care coordination, dietary/nutrition, wound care
- Medication support

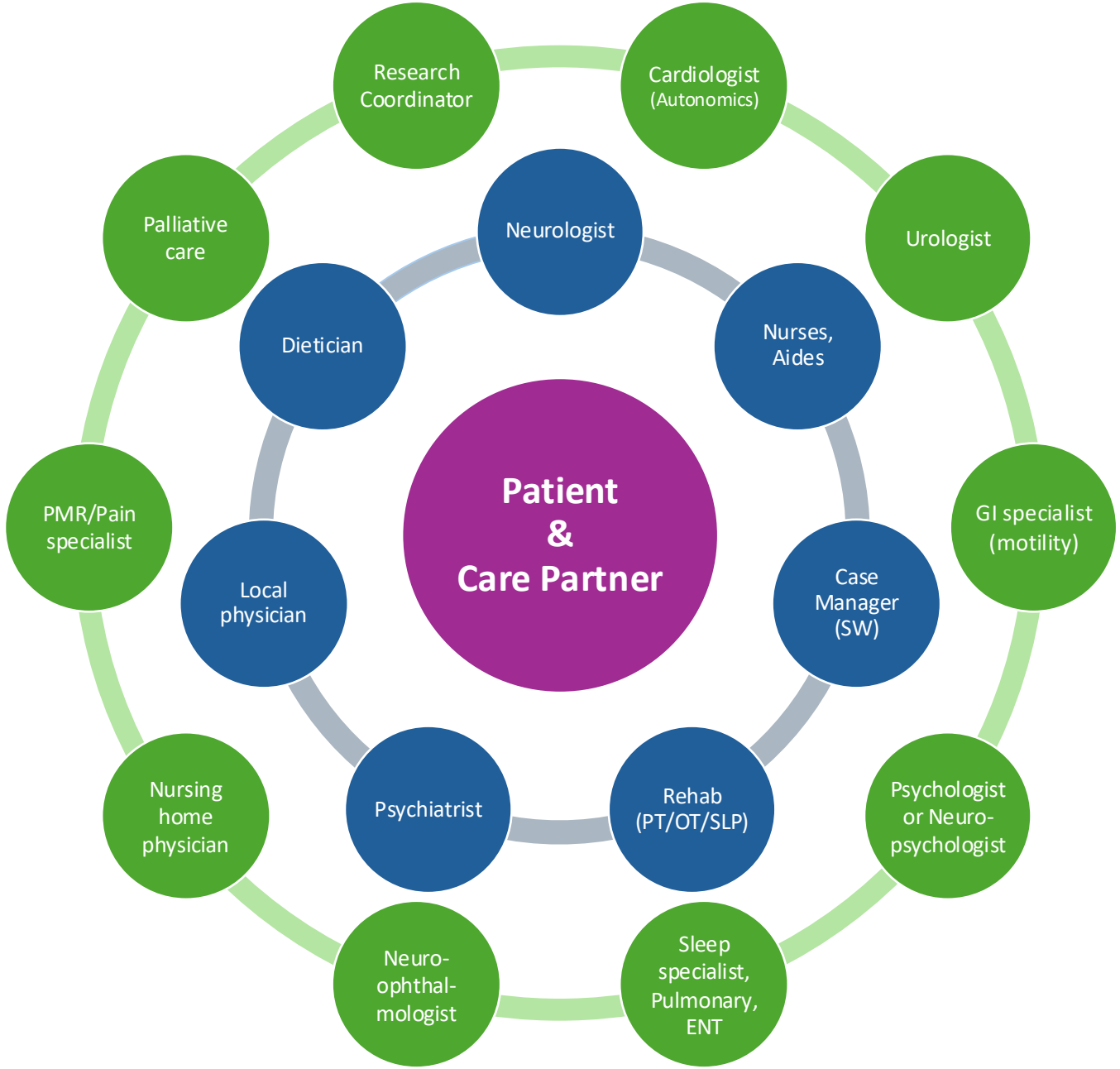
Social services

Treatment of APDs

Requires intra/multidisciplinary team

Patient & care partner in center, the “sun”

Core services, surrounded by support, and ancillary services



Palliative care (not just hospice)

What is it?

- Focus on comfort, quality of life
- Treat pain/suffering
- Emotional well-being
- Psychosocial, spiritual support (patient & caregiver)
- End life on my terms (advanced care planning)



What it's not?

- Not just hospice
- Giving up or "doing nothing"
- Cessation of care
- Stopping all medications
- Losing your doctor (ie. for specialists only)

Summary

1. Not all the looks like PD is PD
2. Atypical Parkinsonisms and “Plus” Syndromes
3. Common pathological hallmarks
4. Treatment differences
5. Interdisciplinary, team approach
6. *Research and new developments*



on Atypical Parkinsonism!

- **A** Autonomic dysfunction
- **F** Falls or freezing of gait (early onset)
- **O** Ocular motor impairment
- **C** Cognitive & Behavioral changes
- **U** Unresponsive to levodopa (poor response)
- **S** Speech & Swallow difficulty (early onset)

Thank you!



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