Updates in PSP

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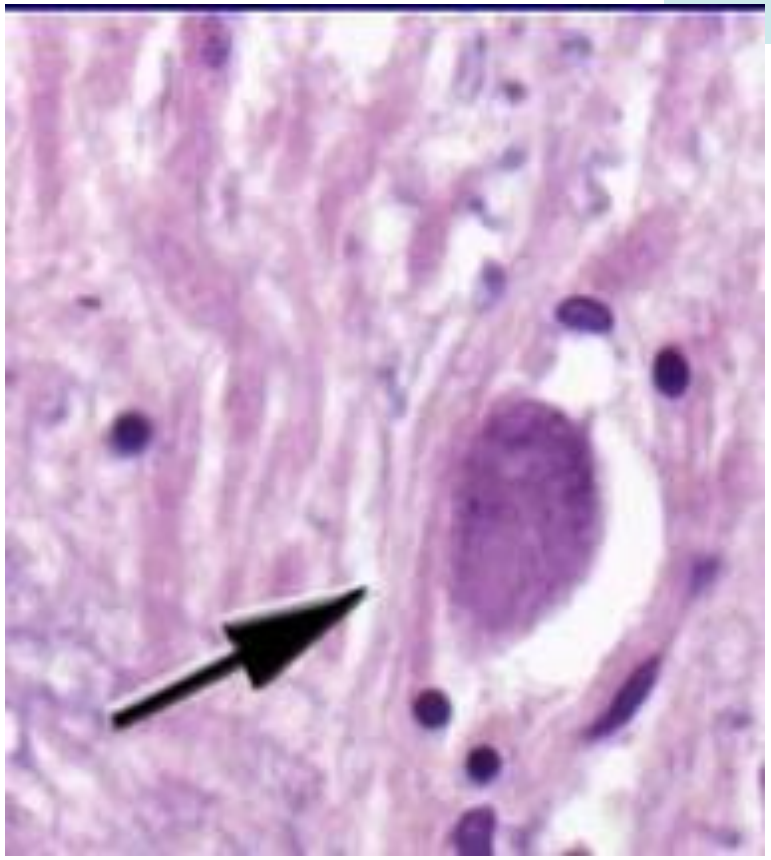
- PSP was first described in 1964 with the leading feature of vertical supranuclear gaze palsy and nerve cell degeneration mainly in the brain stem.

- Then, PSP has been defined by aggregation of the microtubule-associated protein **Tau**, predominantly involving isoforms with four microtubule-binding repeats (4R-tau), in neurofibrillary tangles, oligodendrocytic coils, and, specifically, astrocytic tufts.



National Institute of Neurological Disorders and Stroke Society for PSP (NINDS-SPSP -1996)

- *Criteria*:
  - Mandatory inclusion Criteria
    - Gradually progressive
    - Age over 40
    - Vertical Supranuclear Gaze Palsy
    - Postural instability
  - Mandatory exclusion criteria
    - Any finding showing better explanation
  - Supportive Criteria
    - Symmetric rigidity, axial rigidity, poor L-dopa response, early cognitive / behavioral impairment, early dysphagia or dysartheria
- *Clinical types of PSP:*
  - Definite : Pathologic confirmation
  - Probable : VSP + PI < 1 yr.
  - Possible : VSP or [slow vertical saccades + PI] < 1 yr.

Clinical variants of PSP

- Patients with autopsy-confirmed PSP have been reported with variant PSP clinical presentations, including initial predominance of:
  - ocular motor dysfunction (PSP-OM),
  - postural instability (PSP-PI),
  - Parkinsonism resembling iPD. (PSP-P),
  - frontal lobe cognitive or behavioral presentations (PSP-F), including behavioral variant frontotemporal dementia (bvFTD),
  - progressive gait freezing (PSP-PGF),
  - corticobasal syndrome (PSP- CBS),
  - primary lateral sclerosis (PSP-PLS),
  - cerebellar ataxia (PSP-C),
  - speech/language disorders (PSP-SL):
    - nonfluent/agrammatic primary progressive aphasia (nfaPPA)
    - progressive apraxia of speech (AOS).

- The NINDS-SPSP criteria have excellent specificity :
  - 95% to 100% for probable PSP
  - 80% to 93% for possible PSP.

- the NINDS-PSP criteria's sensitivity is limited (24%) at the first clinical visit.
  - Diagnosis is typically made 3 to 4 years after onset of first symptoms, when the cardinal features, that is falls and supranuclear gaze palsy, have become unequivocally apparent.

- So, early and reliable diagnosis of PSP remains a major clinical challenge :

RESEARCH ARTICLE

Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria

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MDS-PSP Criteria

- Basic features:
  - Mandatory inclusion criteria
  - Mandatory exclusion criteria
- Core clinical features:
  - OPAC
- Supportive features:
  - Clinical Clues
  - Imaging findings

A) Basic features

- need to be present in a patient in order to be considered for the diagnosis of PSP of any phenotype and at any stage :
  - Mandatory inclusion criteria
    - *sporadic,*
    - *adult-onset (age>40),*
    - *gradually progressive neurodegenerative disease.*
  - Mandatory exclusion criteria, rule out PSP and need to be applied in any patient.

Mandatory exclusion criteria / basic features

- *Clinical findings:*
  - Predominant, unexplained impairment of episodic memory, suggestive of AD
  - Predominant, unexplained autonomic failure, e.g., orthostatic hypotension (orthostatic reduction in blood pressure after 3 minutes standing 30 mm Hg systolic or 15 mm Hg diastolic), suggestive of MSA
  - Predominant, unexplained visual hallucinations or fluctuations in alertness, suggestive of LBD
  - Predominant, unexplained multi-segmental upper and lower motor neuron signs, suggestive of MND (pure upper motor neuron signs are not an exclusion criterion)
  - Sudden onset or step-wise or rapid progression of symptoms, in conjunction with corresponding imaging or laboratory findings, suggestive of vascular etiology, autoimmune encephalitis, metabolic encephalopathies, or prion disease
  - History of encephalitis
  - Prominent appendicular ataxia
  - Identifiable cause of postural instability, e.g., primary sensory deficit, vestibular dysfunction, severe spasticity, or lower motor neuron syndrome
- *Imaging findings:*
  - Severe leukoencephalopathy, evidenced by cerebral imaging
  - Relevant structural abnormality, e.g., normal pressure or obstructive hydrocephalus; basal ganglia, diencephalic, mesencephalic, pontine or medullary infarctions, hemorrhages, hypoxic-ischemic lesions, tumors, or malformations

B) Core Clinical Features

- Characteristic clinical manifestations of PSP :
  - Ocular motor dysfunction [O],
  - Postural instability [P],
  - Akinesia [A],
  - Cognitive dysfunction [C].

- each domain, includes 3 characteristic core clinical features, based on levels of certainty :
  - 1 : highest,
  - 2 : mid,
  - 3 :lowest

TABLE 2. Core clinical features

Levels of Certainty	Functional Domain			
	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

Using 12 core clinical features, MDS-PSP is able to diagnose PSP with differing sensitivity and specificity

- *high sensitivity and high specificity* : like Vertical Supra-nuclear palsy (O1)
- *high sensitivity, but reduced specificity*, for example, parkinsonism with tremor and/or asymmetry and/or levodopa responsiveness (A3), needs to presence of other PSP-specific features to qualify for the diagnosis;
- *low sensitivity, but high specificity*, for example, progressive gait freezing within 3 years of symptom onset (P1); a very rare condition, however with a very high positive predictive value for the diagnosis of PSP;
- *low sensitivity and low specificity*, for example, CBS, which is observed regularly in specialized centers and needs to be considered as a possible manifestation of PSP as one of several possible underlying pathologies (C3).

C) Supportive features :

* Have **positive predictive values**,
* Not qualify as diagnostic features, but sufficient to provide helpful ancillary evidence to increase informal diagnostic confidence:

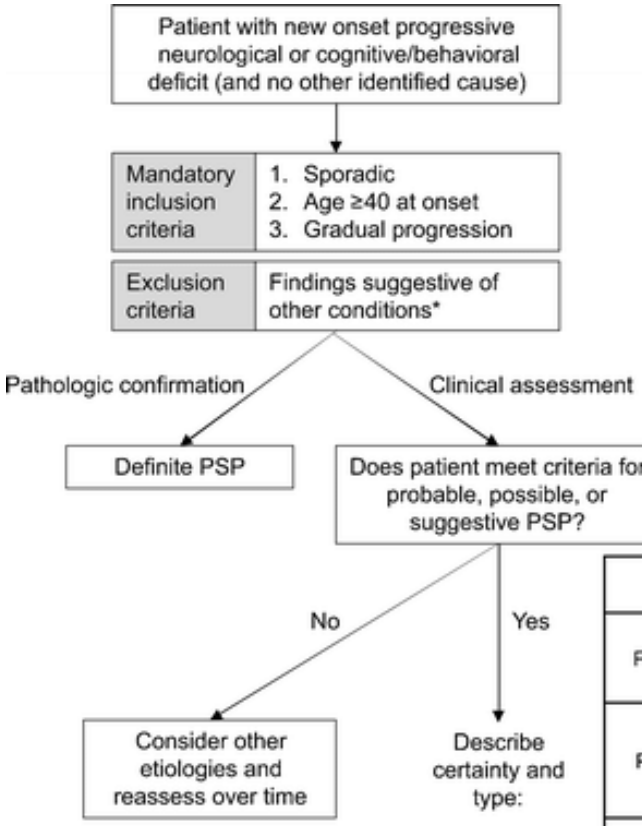
- Clinical Clues:
  - CC1: Levodopa-resistance
  - CC2: Hypokinetic, spastic dysarthria
  - CC3: Dysphagia
  - CC4: Photophobia
- Imaging Findings:
  - IF1: Predominant midbrain atrophy or hypometabolism
  - IF2: Postsynaptic striatal dopaminergic degeneration

TABLE 5. Degrees of diagnostic certainty, obtained by combinations of clinical features and clinical clues

Diagnostic Certainty	Definition	Combinations	Predominance Type	Abbreviation
Definite PSP	Gold standard defining the disease entity	Neuropathological diagnosis	Any clinical presentation	def. PSP
Probable PSP	Highly specific, but not very sensitive for PSP *Suitable for therapeutic and biological studies*	(O1 or O2) + (P1 or P2)	PSP with Richardson's syndrome	prob. PSP-RS
		(O1 or O2) + A1	PSP with progressive gait freezing	prob. PSP-PGF
		(O1 or O2) + (A2 or A3)	PSP with predominant parkinsonism	prob. PSP-P
		(O1 or O2) + C2	PSP with predominant frontal presentation	prob. PSP-F
Possible PSP	Substantially more sensitive, but less specific for PSP *Suitable for descriptive epidemiological studies and clinical care*	O1	PSP with predominant ocular motor dysfunction	poss. PSP-OM
		O2 + P3	PSP with Richardson's syndrome	poss. PSP-RS
		A1	PSP with progressive gait freezing	poss. PSP-PGF
		(O1 or O2) + C1	PSP with predominant speech/language disorder[a]	poss. PSP-SL
		(O1 or O2) + C3	PSP with predominant CBS[a]	poss. PSP-CBS
Suggestive of PSP	Suggestive of PSP, but not passing the threshold for possible or probable PSP *Suitable for early identification*	O2 or O3	PSP with predominant ocular motor dysfunction	s.o. PSP-OM
		P1 or P2	PSP with predominant postural instability	s.o. PSP-PI
		O3 + (P2 or P3)	PSP with Richardson's syndrome	s.o. PSP-RS
		(A2 or A3) + (O3, P1, P2, C1, C2, CC1, CC2, CC3, or CC4)	PSP with predominant parkinsonism	s.o. PSP-P
		C1	PSP with predominant speech/language disorder	s.o. PSP-SL
		C2 + (O3 or P3)	PSP with predominant frontal presentation	s.o. PSP-F
		C3	PSP with predominant CBS	s.o. PSP-CBS

The **basic features B1+B2+B3** (see Table 1) apply for all probable, possible, and suggestive criteria. Core **clinical features** are defined by their functional domain (ocular motor dysfunction [**O**], postural instability [**P**], akinesia [**A**], and cognitive dysfunction [**C**]), and stratified by presumed levels of certainty (**1** [highest], **2** [mid], **3** [lowest]) they contribute to the diagnosis of PSP (see Table 2). Supportive **clinical clues** (CC) are presented in Table 3. Operationalized definitions of clinical features and clinical clues are given in Table 4.

[a]Probable 4R-tauopathy (i.e., either PSP or CBD).



Predominance Type

	PSP-RS	PSP-PGF	PSP-P	PSP-F	PSP-OM	PSP-SL	PSP-CBS	PSP-PI
Probable	(O1 or O2) + (P1 or P2)	(O1 or O2) + A1	(O1 or O2) + (A2 or A3)	(O1 or O2) + C2				
Possible	O2 + P3	A1			O1	(O1 or O2) + C1	(O1 or O2) + C3	
						Probable 4R-tauopathy		
Suggestive	O3 + (P2 or P3)		(A2 or A3) + (O3, P1, P2, C1, C2, CC1**, CC2, CC3, or CC4)	C2 + (O3 or P3)	O2 or O3	C1	C3	P1 or P2

Predominance Clinical Types

- Are determined based on the combination of clinical features:
  - Include:
    - PSP-RS, PSP-OM, PSP-PI, PSP-P, PSP-F, PSP-PGF, PSP-CBS, PSP-SL
    - (Patients with possible PSP-SL or PSP-CBS also qualify for the diagnosis of a probable 4R-tauopath)

Some conclusions for the MDS-PSP criteria:

- 1- Genetic analyses do not help to support the clinical diagnosis of PSP, but known rare genetic mutations in some genes are exclusion criteria, because they may mimic aspects of PSP clinically, but differ neuropathologically.

- 2 - Established fluid biomarkers do not help to support the clinical diagnosis of PSP, but can rule out alternative non-neurodegenerative diagnoses in patients with similar clinical presentations.
  - CSF bio-markers for AD may be useful in research investigations and help exclude patients with underlying AD.
- 3 - Brain imaging is relevant to rule out alternative diagnoses.
  - Demonstration of predominant midbrain atrophy or hypometabolism and/or postsynaptic striatal dopaminergic degeneration increases the diagnostic confidence in patients diagnosed on the basis of clinical features and qualifies for the label of “imaging supported diagnosis.”

Structural Brain MRI

demonstrating the morphological characteristics of PSP-RS and brain stem measurements

Top left sagittal slice shows the hummingbird sign with atrophy of the dorsal midbrain and relative preservation of the pons.

Top right axial slice through the midbrain shows rounded midbrain peduncles (Mickey Mouse sign) and concavity of the lateral margin of the midbrain Tegmentum (morning glory sign [arrow])

FDG-PET, DAT, and tau PET findings in PSP-RS

(A) FDG-PET scan for a PSP-RS patient: Hypo-metabolism is observed in the frontal lobes, midbrain, and caudate nucleus.

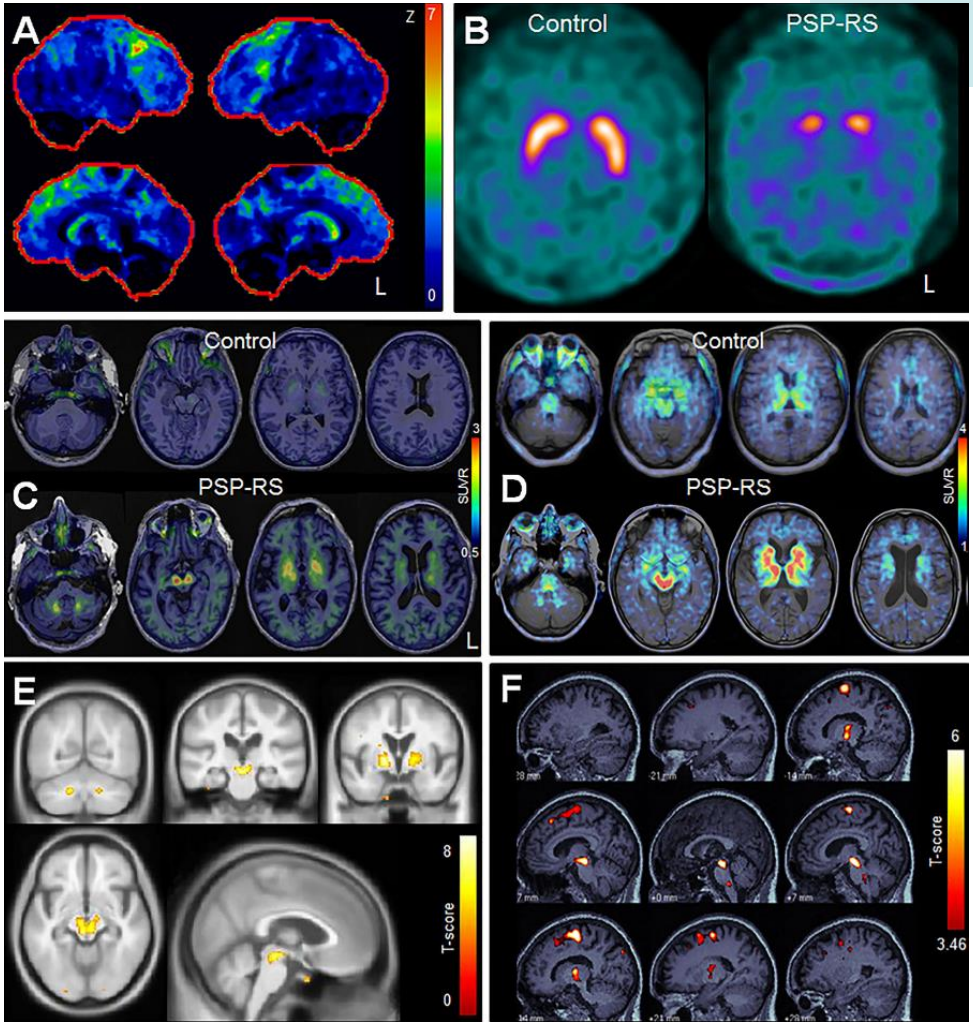
(B) DAT scan: Absent putamen DAT binding and reduced caudate binding in PSP-RS compared with a control subject.

(C) [18F]AV-1451 tau-PET scan: greater uptake in midbrain and basal ganglia regions in the PSP- RS patient compared to control cases. In addition, the PSP-RS patient shows uptake in the dentate nucleus of the cerebellum and thalamus.

(D) THK-5351 tau-PET scan: greater uptake in PSP-RS in the thalamus and basal ganglia

(E) Group-level [18F]AV-1451: Increased uptake in PSP-RS compared with controls in dentate nucleus of the cerebellum, midbrain, thalamus, and basal ganglia

(F) Group-level THK-5351: Increased uptake in PSP-RS compared with controls is identified in midbrain, thalamus, basal ganglia, and posterior lateral and medial frontal lobes.



MANAGEMENT

Management of motor parkinsonism in PSP

- 1. Levodopa trial
  - a. Helpful only when bradykinesia, rigidity or tremor affects daily activities.
  - at least 1 month to 900–1,200mg per day.
  - c. Maintain maximum tolerated dosage for at least 1 month.
  - d. If no benefit, or if adverse effects (including dyskinesias) occur, gradually taper over at least 2 weeks and try to discontinue.
- 2. Dopaminergic medications are unnecessary and should be avoided
  - a. Avoid “controlled-release” and “extended-release” preparations
  - b. Avoid dopamine receptor agonists
  - c. Avoid monoamine oxidase B inhibitors
  - d. Avoid catecholamine O-methyltransferase inhibitors
  - e. Avoid adenosine A2A receptor antagonists
- 3. Anticholinergics should be avoided.

- **Donepezil** was found to worsen motor symptoms while improving cognitive function in PSP patients in a randomized, double blind, placebo-controlled crossover trial.
- **Amitriptyline** Despite some retrospective reports of clinically improvement in motor function on low doses, currently not recommended in PSP because of its anticholinergic side effects and risk of exacerbating falling.
- **Coenzyme Q-10** in its liposomal formulation at a dosage of 100mg tid gave modest but statistically significant benefit in the PSP Rating Scale, mostly in the gait and balance items, in a 6-week double-blind trial.
- A double-blind, placebo-controlled crossover study in 10 PSP patients receiving single doses of zolpidem, carbidopa/levodopa, or placebo showed no difference between carbidopa/levodopa and placebo, but patients on **zolpidem** 5mg showed a 6.5% improvement in the UPDRS-III over baseline, a statistically significant result.

- Surgical approach

  - The effects of deep brain stimulation of the globus pallidus pars interna and subthalamic nucleus on Parkinsonism, gait difficulty, and balance in PSP have failed to show convincing benefit
  - Pedunculopontine nucleus DBS is still being investigated in PSP, but to date has shown modest and inconsistent benefit as well.
  - Spinal cord stimulation for freezing of gait in PSP is under study.

Management of Gait dysfunctions in PSP

- 1.Pharmacologic therapy
  - a. Amantadine
    - i. Start at 50–100mg daily and titrate at intervals of at least 2 weeks
    - ii. Do not exceed 100mg TID.
    - iii. Monitor for psychosis, confusion, and constipation.
    - iv. Inspect for livedo reticularis and reassure patient that it is benign.
  - b. Coenzyme Q-10
    - i. Modest benefit on average but some patients respond well
    - ii. Use liposomal form (a liquid) at 100mg TID
    - iii. If no benefit after 2 months, discontinue.
- 2.Non-pharmacologic therapy
  - a. Physical therapy
    - i. Early intervention recommended
    - ii. Focused on postural stability and gait re-training
    - iii. Balance, eye movement training and visual awareness training may help.
  - b. Exercise
    - i. Aerobic exercise
      - 1. If tolerated and safe
      - 2. Obtain approval from PCP or cardiologist if cardiovascular history is present.
    - ii. Recumbent bicycle.
  - c. Assistive devices
    - i. Cane should be prescribed with caution
      - 1. Tripping hazard, as patients tend to carry cane hanging from wrist
      - 2. Fails to prevent falls in other directions.
    - ii. Weighted walker
    - iii. Wheelchair
    - iv. A lightweight transport wheelchair is useful when the caregiver cannot lift a standard wheelchair into a car's trunk.

Management of Dystonia in PSP

- 1. Pharmacologic therapy
  - a. Baclofen started at 5mg daily, titrating gradually to no more than 10mg TID
  - b. Clonazepam starting at 0.25mg daily, titrating gradually to no more than 3mg daily
  - c. Trihexyphenidyl not recommended due to central and peripheral anticholinergic side effects
  - d. BoNT injections are the most effective treatment for focal dystonia

- 2. Non-pharmacologic therapy
  - a. No formal studies demonstrate benefit of physical therapy for dystonia in PSP.
  - b. Occupational therapy may be beneficial for dystonia in PSP.
    - (i) Home health assessment
    - (ii) Evaluation for orthoses such as splints/braces
    - (iii) Exercises to optimize upper limb function

Management of eyelid and visual dysfunctions in PSP

- 1. Pharmacologic therapy
  - a. BoNT injections recommended for blepharospasm/lid levator inhibition
    - i. EMG guidance not necessary or recommended
    - ii. Pretarsal injections only recommended for refractory cases
  - b. Improve tear volume
    - i. Artificial tears
      - 1. Glycerin
      - 2. Carboxymethylcellulose
      - 3. Polyethylene glycol
    - ii. Preservative-free lubricants
- 2. Non-pharmacologic therapy
  - a. Eyelid crutches
  - b. Sensory trick eyewear frames
  - c. Prevent conjunctival drying with humidifiers, warm wet compresses, avoiding forced air ventilation, and protective eyewear
  - d. Binocular prisms
    - i. For gaze limitation, not for diplopia
    - ii. Use with caution during ambulation
  - e. Environmental modifications
    - i. Elevate dinner plate
    - ii. Remove loose rugs, low coffee tables, and children's toys from floors
    - iii. Follow dinner fork or finger down to target
  - f. Referral to ophthalmologist or neuro-optometrist for consideration of:
    - i. Measures to reduce inflammation related to drying
    - ii. Improve tear retention

Management of Constipation in PSP

- 1. Non-pharmacologic therapy
  - a. Increased physical activity
  - b. Adequate hydration until suppertime to minimize nocturnal trips to void
  - c. Fiber supplementation
  - d. Minimize
    - i. Anticholinergics
    - ii. Amantadine
    - iii. Opiates
- 2. Pharmacologic therapy
  - a. Stool softener, docusate starting at 100mg daily titrated weekly to 100mg TID
  - b. Osmotic laxatives
    - i. Polyethylene glycol
    - ii. Magnesium citrate
    - iii. Lactulose
    - iv. OTC enema preparations of saline or other hyperosmolar salts
  - c. Stimulants *for very short-term use*
    - i. Bisacodyl
    - ii. Senna
  - d. Prescription medications for refractory cases
    - i. Linaclotide (guanylate cyclase C agonist)
    - ii. Prucalopride (selective 5-HT4 receptor agonist)

Management of Urinary dysfunction

- Pharmacologic therapy for overactive bladder
  - a. Alpha-receptor antagonists
    - i. Terazosin
    - ii. Doxazosin
    - iii. Tamsulosin
    - iv. Alfuzosin
    - v. Silodosin
  - b. 5-alpha reductase inhibitors
    - i. Finasteride
    - ii. Dutasteride
  - c. Beta-3 adrenoceptor agonists
    - i. Mirabegron
    - ii. Vibegron
  - d. Selective M3 anti-muscarinic anticholinergics
    - i. Darifenacin
    - ii. Solifenacin
  - e. Avoid non-selective anti-muscarinic agents due to central anticholinergic side effects
    - i. Avoid oxybutynin
    - ii. Avoid tolterodine
    - iii. Avoid fesoterodine
    - iv. Trospium has limited brain penetration and may be considered
  - f. BoNT injections for refractory overactive bladder

- Non-pharmacologic therapy
  - a. Alcohol and caffeine avoidance
  - b. Nocturia
    - i. Compression stockings during day
    - ii. Elevate lower limbs in the late afternoon
    - iii. Restrict fluids in the evening
    - iv. Fully empty bladder before bed
    - v. Elevate the head of the bed at night
    - vi Bladder training and pelvic floor exercises
  - c. Condom catheter for men
  - d. Clean intermittent catheterization for refractory urinary voiding dysfunction with residual volume over 100mL.
  - e. Trans-tibial nerve stimulation

Management of Sleep disturbance-Pharmacological

- 1. Pharmacologic therapy for **insomnia**
  - a. Melatonin (3–18mg nightly)
  - b. Low dose clonazepam (0.25–1mg nightly)
  - c. Other benzodiazepines, benzodiazepine receptor agonists
    - i. Zolpidem
    - ii. Eszopiclone
    - iii. OTC sleep aids such as diphenhydramine and others
  - d. Atypical and tricyclic antidepressants should be avoided or used with extreme caution
- 2. Pharmacologic therapy for **excessive daytime somnolence**
  - a. Stimulants such as modafinil, armodafinil, or methylphenidate
  - b. Use these at low dosages
- 3. Pharmacologic therapy for **RLS**/PLMD
  - a. Iron replacement (ferrous sulfate 325mg daily with Vitamin C) if serum ferritin < 75 mcg/l
  - b. Gabapentin
  - c. Pregabalin
  - d. Dopamine agonists
    - i. Pramipexole
    - ii. Ropinirole
    - iii. Rotigotine
    - iv. Cabergoline
- 4. Pharmacological therapy for **REM behavioral disorder**
  - a. Melatonin (3–18mg nightly)
  - b. Low dose clonazepam (0.25–1mg nightly)
  - c. Gabapentin (100–300mg nightly)

Management of Sleep disturbance, Non-Pharmacological

- 1. Non-pharmacologic therapy for insomnia
  - a. Circadian alignment
  - b. Sleep hygiene
  - c. Treatment of underlying issues
    - i. Depression
    - ii. Immobility
    - iii. Nocturia

- 2. Non-pharmacologic therapy for obstructive sleep apnea
  - a. Lateral decubitus positioning during sleep
  - b. Weight loss in the setting of obesity
  - c. Elevating the head of the bed
  - d. Splinting with oral appliances
  - e. Continuous positive airway pressure
  - f. Surgical removal of obstructive tissue
  - g. Activation of tongue protrusion by implantation of a hypoglossal nerve stimulator

Dysphagia in PSP

- Patients with PSP often have impairments of both the oral and pharyngeal phases of swallowing.
- Signs and symptoms associated with dysphagia in PSP can include:

  - delayed swallow initiation,
  - disorganized, or hyperkinetic tongue movements,
  - slowing of the oral phase,
  - prolonged mastication
  - Poor transfer of the bolus to the pharynx
  - vallecular pooling,
  - incomplete epiglottic descent.

Management of sialorrhea and dysphagia in PSP

- 1. Pharmacologic therapy for sialorrhea
  - a. BoNT injections are first line therapy
  - b. Oral glycopyrrolate (monitor for anticholinergic effects)
  - c. Sublingual atropine drops not recommended because of central anticholinergic effects
- 2. Non-pharmacologic therapy for dysphagia
  - a. Conservative measures
    - i. Postural maneuvers (chin-tuck posture, head turns)
    - ii. Alternating small bites and sips
    - iii. Taking multiple swallows
    - iv. Volitional coughing and throat-clears after swallowing
    - v. Breath-hold or supraglottic swallow
    - vi. As suggested by results of modified barium swallow
      - 1. Thickening liquids to nectar or honey-thick consistency
      - 2. Avoiding dry solids or mixed consistencies
  - b. Early speech language pathology referral
  - c. Tube feedings/percutaneous gastrostomy
    - i. Reserve for severe cases
    - ii. Carefully consider ethical and quality-of-life issues.

Con. (Management of Dysphagia)

- Medications like Levodopa do not typically benefit dysphagia in PSP.
- For levodopa-responsive patients with PSP-Parkinsonism, dosing levodopa approximately half an hour before mealtimes may modestly aid feeding and swallowing

Management of speech impairment in PSP

- 1. Dysarthria
  - a. Speech therapy to maximize comprehensibility
  - b. Augmentative and alternative means of communications as disease progresses
    - i. Delayed auditory feedback or pacing boards
    - ii. Alphabet board
    - iii. Text-to-speech system
    - iv. Eye-gaze speech-generating devices
    - v. Eye-gaze speech-generating devices
- 2. Apraxia of speech
  - a. Intense, repetitive exercises
  - b. Metronome and other pacing methods
  - c. Gesture
  - d. Writing
  - e. Experimental: cerebellar repetitive transcranial magnetic stimulation
- 3. Non-fluent aphasia
  - a. Exercises to improve pace of speech
  - b. Gesture and other non-speech modalities
  - c. Caregiver and family determine topic and tone of conversation
  - d. Experimental: dorsolateral prefrontal cortical transcranial direct current stimulation
- 4. Palilalia
  - a. Pacing board
  - b. Metronome and other pacing methods

Behavioral and cognitive dysfunctions in PSP

- Behavioral and cognitive symptoms are the presenting feature in ~20% of PSP patients.
- The principal cognitive impairments of PSP affect abstract thought and verbal fluency, while forgetfulness and visuospatial issues are mild to moderate until advanced disease stages.
- The prevalence of executive dysfunction can be as high as 30% in the pre-diagnostic phase of PSP, and others have demonstrated this disturbance early in the disease course in more than 70% of patients.

Management of cognitive impairment in PSP

- 1. Pharmacological management
  - a. Cholinesterase inhibitors such as donepezil
    - 1. Use only for amnestic deficits
    - 2. Avoid in cases of severe postural instability
    - 3. Discontinue if no observed benefit
- 2. Non-pharmacological management
  - a. Caregiver and family education
  - b. Maintain a daily routine
    - 1. Adapt previous activities to reduced abilities
    - 2. Emphasize enjoyable, rather than therapeutic, activities
    - 3. Minimize distractors
    - 4. Occupational therapy
      - 1. Safety screening
        - a. Medication management
        - b. Financial risk
      - 2. Access to stove, car, firearms
  - c. Compensatory technology
    - 1. Daily planners
    - 2. Mobile devices
  - d. Lifestyle modifications
    - 1. Aerobic exercise
    - 2. Heart-healthy diet
    - 3. Adequate sleep and nutrition
    - 4. Staying cognitively and socially engaged

Management of behavioral disturbances in PSP

- 1. Pharmacologic management
  - a. **Apathy**:
    - i. Trial of modafinil or methylphenidate
  - b. **Impulsivity**
    - i. Behavioral approaches difficult because of frontal deficit.
    - ii. Reduce levodopa and other dopaminergic medications
    - iii. Trial of SSRI such as escitalopram or sertraline at standard dosages
    - iv. Mood stabilizers such as valproic acid and lamotrigine
    - v. ADHD drugs such as atomoxetine
  - c. **Depression**/Mood disorder
    - i Trial of SSRI at standard dosages
    - ii Avoid tricyclic antidepressants due to side effects
  - d. **Pseudobulbar** affect
    - i. Trial of SSRI at standard dosages
    - ii. Dextromethorphan-quinidine (second-line due to cost)
- 2. Non-pharmacologic management
  - a. Caregiver/family education emphasizing that deficit is part of disease
  - b. Occupational therapy
  - c. Cognitive behavioral therapy
  - d. Safety screening
    - i. Risk of medication mismanagement,
    - ii. Financial risk
    - iii. Use of a stove
    - iv. Driving
    - v. Exposure to unsecured firearms

Apraxia

- Apraxia is defined as a deficit of motor programming that affects the performance of a learned skilled movement and is not caused by deficits in other cognitive, sensory, or motor domains

Management of limb apraxia in PSP

- 1. Identify and address other factors impairing performance
  - a. Motor deficits
  - b. Cognitive deficits
  - c. Occupational therapy
    - i. Evaluate for environmental changes
    - ii. Simplify tasks to reduce the need for manual dexterity
    - iii. Gestural, direct and explorative training
    - iv. Encourage bimanual or bipedal tasks for asymmetric motor neglect or alien limb
    - v. Mirror therapy
    - vi. Repetitive facilitation exercise and video game-based rehabilitation

Experimental neuroprotective approaches and clinical trials for PSP

- 1. Completed clinical trials (none has shown clinical efficacy)
  - a. Riluzole (multiple proposed mechanisms of action)
  - b. Davunetide (microtubule stabilizer)
  - c. Tideglusib (GSK-3 beta inhibition to reduce hyperphosphorylation)
  - d. Monoclonal antibodies directed against N-terminal of tau
- 2. Novel neuroprotective approaches in or near clinical trials
  - a. RT001 (anti-lipid peroxidation agent)
  - b. UCB0107 (anti-tau antibody targeting the microtubule binding domain rather than the N-terminal)
  - c. ASN120290 (O-GlcNAcase inhibitor to inhibit removal of O-linked N-acetylglucosamine from tau)
  - d. AZP2006 (increases progranulin)
  - e. MP201(mitochondrial uncoupler)
  - f. Tolfenamic acid (NSAID and tau transcription factor Sp1 inhibitor)
  - g. Antisense oligonucleotides (reduce tau production)

Thanks for your attention