Understanding Progressive Supranuclear Palsy (PSP)

David Shprecher, DO FAAN

Movement Disorders Director

Banner Sun Health Research Institute

- **"I understand that one person in 100,000 suffers from the disease and I am also aware that there are 100,000 members of my union, the Screen Actors Guild, who are working every day."**
- **"I think, therefore, it is in some way considerate of me that I have taken on the disease for myself, thus protecting the remaining 99,999 members from this fate."**

Key Points

- PSP as the 2nd most common neurodegenerative cause of parkinsonism
- PSP diagnosis based on symptoms and not a specific test
- Treatments to ease the burden of PSP
- Hope for the future through research

Banner Research

What is “Parkinsonism?”

- 2/4 Cardinal Symptoms
  - Tremor
  - Bradykinesia (Slowness of movement)
  - Rigidity (Stiffness, or resistance of the limbs to passive movement)
  - Postural Instability (Impaired balance)

Banner Research

Signs of atypical parkinsonism in the first 3 yrs

- Dementia with cognitive fluctuations, Hallucinations, Dream enactment
  - Dementia with Lewy bodies (DLB)
- Fainting, Incontinence, Ataxia
  - Multiple system atrophy (MSA)
- Severe loss of hand control on one side
  - Corticobasal degeneration (CBD)

Banner Research

Signs of atypical parkinsonism in the first 3 yrs

- Recurrent severe falls, trouble moving eyes vertically, frontotemporal dementia (language problems, profound changes in behavior)
  - Progressive Supranuclear Palsy (PSP)
- Pure lower body symptoms
  - Vascular parkinsonism or NPH
    - NOT neurodegenerative
    - Can co-exist with other conditions
    - Require brain MRI or CT scan to diagnose
  - PSP- *pure akinesia gait freezing variant*

Banner Research

Key Features of Atypical Parkinsonian Disorders

	PSP	CBD	MSA	DLB	Vascular
Early Falls	++++	+/-	+/-	+/-	++
Gaze palsy	+++	++	+/-	+/-	+/-
Dementia	+/-	+/-	+/-	+++	+/-
Psychosis	-	-	-	+/-	-
RBD	-	-	+++	++	-
Pathology	Tau	Tau	GCI	LB	vascular

PSP= progressive supranuclear palsy; CBD= corticobasal degneeration; MSA= multiple system atrophy; DLB= dementia with Lewy bodies; RBD= REM sleep behavior disorder; tau= microtuble associated protein tau; GCI= alpha-synuclein glial cytoplasmic inclusions; LB- Lewy bodies (alpha-syuclein, ubiquitin)

Banner Research

The Classic PSP Triad

- Vertical gaze problems
- Postural Instability
- Atypical parkinsonism
  - rigid neck
  - similar symptoms on both sides
  - Poor or waning response to levodopa
- 98.5% of classic cases do have PSP

Lopez et al. Accuracy of four clinical diagnostic criteria for the diagnosis of neurodegenerative dementias. Neurology. 1999 Oct 12;53(6):1292-9. doi: 10.1212/wnl.53.6.1292. PMID: 10522887

PSP Sub-Types

- PSP-RS (Richardson syndrome)
- PSP-P (Parkinsonian variant)
- PSP-PGF (Progressive Gait Freezing)
- PSP-F (frontotemporal dementia)
- PSP-PI (Postural instability predominant)
- PSP-CBS (Corticobasal syndrome)
- PSP-SL (speech language predominant)

Hoglinger et al. Clinical Diagnosis of Progressive Supranuclear Palsy: The Movement Disorder Society Criteria. 2017. DOI: 10.1002/mds.26987

Banner Research

Diagnosis of PSP

- Probable vs Possible (confidence levels)
- Based on characteristic features
  - Vertical Eye movement Abnormalities
  - Parkinsonism
  - Postural Instability
  - Frontotemporal dementia type cognitive impairment

Banner Research

Supportive tests

- MRI
  - May show characteristic features of PSP (“morning glory sign”) or MSA
  - May raise concern for normal pressure hydrocephalus or vascular parkinsonism
- Syn One Biopsy test
  - Positive test doesn’t rule PSP out (10% of Parkinson’s also have PSP)
  - Negative test may help improve diagnostic confidence in less common presentations
- DaTscan
  - Negative test may suggest motor neuron disease

Banner Research

Common Symptoms of PSP

- Cognitive (frontotemporal dementia)
- Blepharospasm, eyelid opening apraxia
- Behavioral
  - Involuntary Emotional Expression, anxiety
- Insomnia, RLS
- Swallowing problems
- Speech and language problems
- Constipation, bladder incontinence

Banner Research

PSP Prognosis

- Wheelchair dependency due to repeated falls: 3-4 years
- Severe swallowing problems 5.6 y
- Incontinence 5.8y
- Severe cognitive impairment 5.9 y
- Lifespan from start of symptoms: 5-8 y

Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. Lancet Neurol. 2009 Mar;8(3):270-9.

Mahale et al. Subtypes of PSP and Prognosis: A Retrospective Analysis. Ann Indian Acad Neurol. 2021 Jan-Feb;24(1):56-62

Banner Research

Standard PSP Treatments

- Parkinsonism- Carbidopa/levodopa
  - 1200 mg per day (or max tolerated dose)
- Gait Freezing
  - Amantadine
- Postural Instability
  - Physical therapy (limited duration of benefit)
- Involuntary Emotional Expression
  - Nuedexta (dextromethorphan/quinidine)

Bluett et al. Best Practices in the Clinical Management of Progressive Supranuclear Palsy and Corticobasal Syndrome: A Consensus Statement of the CurePSP Centers of Care. Front Neurol. 2021 Jul 1;12:694872. doi: 10.3389/fneur.2021.694872. PMID: 34276544

Banner Research

Standard PSP Treatments

- Blepharospasm, excess saliva
  - Botulinum toxin injections
- Insomnia
  - Trazodone, mirtazapine
- Bladder Incontinence
  - AVOID oxybutynin
- RLS
  - gabapentin, Horizant (gabapentin enacarbil), pregabalin, ropinirole, pramipexole, Neupro (rotigotine)

Bluett et al. Best Practices in the Clinical Management of Progressive Supranuclear Palsy and Corticobasal Syndrome: A Consensus Statement of the CurePSP Centers of Care. Front Neurol. 2021 Jul 1;12:694872. doi: 10.3389/fneur.2021.694872. PMID: 34276544

Important Care Considerations

- Movement Disorders Specialists
- Telemedicine
- Multidisciplinary Care
- Advance Care Planning and Caregiver Burden

Bluett et al. Best Practices in the Clinical Management of Progressive Supranuclear Palsy and Corticobasal Syndrome: A Consensus Statement of the CurePSP Centers of Care. Front Neurol. 2021 Jul 1;12:694872. doi: 10.3389/fneur.2021.694872. PMID: 34276544

Banner Research

When to consider genetic testing

- First degree relative with motor neuron disease, FTD: **C9orf72**
- First degree relative with PSP
  - Progranulin, MAPT, LRRK2
- Genetic testing is NOT covered by Medicare
  - You may want to pay for it if you have descendants and want them to know what you really had

Banner Research

Hope through Research

- Earlier, more accurate diagnosis
- Understanding the cause of PSP
- Treatments for symptoms
- Efforts at slowing the disease

Banner Research

Genetic Discoveries from PSP Brain Donation

- Recent studies suggested slight increases in risk from a few other genes.
  - Syntaxin-6, EIF2AK3, and MOBP
  - MOBP (myelin associated oligodendrocyte protein) linked to CBD and PSP
  - N-acetyltransferase 2 rapid acetylator phenotype is associated with PSP, suggesting it may be responsible for activation of a xenobiotic whose metabolite is neurotoxic

Höglinger et al. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat Genet. 2011 Jun 19;43(7):699-705.

Kouri et al. Genome-wide association study of corticobasal degeneration identifies risk variants shared with progressive supranuclear palsy. Nat Commun. 2015 Jun 16;6:7247.

Polymorphic genes of detoxification and mitochondrial enzymes and risk for progressive supranuclear palsy: a case control study. BMC Med Genet. 2012 Mar 17;13:16.

Banner Research

Studies to Improve diagnosis

- PI-2620 binds the tau protein
- Lights up on PET scans to accurately diagnose classic PSP
- People with any advanced neurodegenerative illness can volunteer in the Life Molecular Imaging study- https://life-mi.com/advance-study/

Banner Research

Treatments that did NOT slow progression of PSP

- Antioxidants
  - coenzyme Q10, rasagiline, RT-001
- Microtubule stabilizer davunetide
- Anti-tau antibodies
  - BIIB092, ABBV-8E12

Banner Research

Studies of treatments designed to slow progression

- AMX0035 (sodium phenybutyrate/aturursodiol)
  - Targets endoplasmic reticulum stress and mitochondrial dysfunction
  - https://www.amylyxpsptrial.com/
- FNP-223 (ASN90)
  - Aims to block tau aggregation
  - Look up PROSPER trial online
- Additional trials may be listed soon on Clinicaltrials.gov

Banner Research

Observational PSP Research

- Anyone with atypical parkinsonism can sign up for the CURE PSP brain donation program- https://www.psp.org/brain-donation-program
- Because unusual presentations of PSP can only be confirmed with an autopsy
  - This program gives your family a definite answer of what you had
  - Genetic research into the cause of PSP can be done from this program

Banner Research

Key Points

- PSP is a prime of life illness that is likely under diagnosed
- PSP diagnosis requires expert history and exam (and may require autopsy to confirm)
- Multidisciplinary care and advanced planning can ease the burden of PSP
- There is hope for the future through research

Banner Research