Progressive supranuclear palsy (PSP)
Spectrum of clinical manifestations

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Talk objectives

• PSP- diagnosis
• Spectrum of clinical manifestations
• Approach to PSP management
  – Pharmacological Tx
  – Supportive care
PSP - first reported 1964

- 9 cases
  - 7 with neuropathology

PARKINSONISM

- Tremor resting
- Rigidity
- Akinesia / bradykinesia
- Postural instability*

6/27/2017
Parkinsonism
CLASSIFICATION

- Idiopathic PD
- Symptomatic parkinsonism
- Neurodegenerative diseases
- Other disorders with parkinsonian signs

NEURODEGENERATIVE Ds

- Progressive Supranuclear Palsy
- Multiple System Atrophy
- Cortical- Basal Degeneration
- Diffuse Lewy body Disease
- Other
Progressive Supranuclear Palsy

Clinical features
Onset after age 40
- Progressive course
- Parkinsonism
- Severe postural instability
- Supranuclear gaze palsy
- Dysarthria, dysphagia

PSP epidemiology
- Prevalence 3-6/100,000
- Age of onset mid 60s
- Ultimate diagnosis – pathology based

Figure 1: Tau immunohistochemistry using anti-tau (AT8) antibody shows lighted astrocytes in the frontal cortex of a case with pathologically confirmed progressive supranuclear palsy (c. 20 magnifications)
PSP diagnostic criteria
Litvan et al 1996

- Possible
  - Progressive Ds onset >40 y.o.
  - Either vertical gaze palsy or prominent postural instability in first year of Ds

- Probable
  - Above and both vertical gaze palsy and PI

- High specificity but low sensitivity

- Definite- histopathology proven
  - Tau (+) Neurofibrillary tangles / straight filaments
• Literature review 1996-2015
  – N=5903 articles
    • N=462 REVIEWED
  – Review of the largest autopsy confirmed cases
    • N=206 + N= > 200 other degenerative conditions

Spectrum of PSP syndromes

PSP-PI
PSP-PGF
PSP-OM
PSP-AOS
PSP-P
PSP-CBG
PSP-F/bvFTD
PSP-SL
PSP-RS
24%
76% non classical presentation

Höglinger et al, MDS-PSP study group 2017
Spectrum of PSP symptoms

- Oculomotor dysfunction
- Postural instability
- Cognitive dysfunction
- PSP-RS
- Akinesia

Haglinger et al, MDS-PSP study group 2017

PSP-core clinical features

<table>
<thead>
<tr>
<th>Levels of Certainty</th>
<th>Ocular Motor Dysfunction</th>
<th>Postural Instability</th>
<th>Akinesia</th>
<th>Cognitive Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Q1: Vertical supranuclear gaze palsy</td>
<td>P1: Repeated unprovoked falls within 3 years</td>
<td>A1: Progressive gait freezing within 3 years</td>
<td>C1: Speech/language disorder, i.e., nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech</td>
</tr>
<tr>
<td>Level 2</td>
<td>Q2: Slow velocity of vertical saccades</td>
<td>P2: Tendency to fall on the pull-test within 3 years</td>
<td>A2: Parkinsonism, akinesic rigid, predominantly axial, and levodopa resistant</td>
<td>C2: Frontal cognitive/behavioral presentation</td>
</tr>
<tr>
<td>Level 3</td>
<td>Q3: Frequent macro square wave jerks or &quot;nystagmus apraxia&quot;</td>
<td>P3: More than two steps backward on the pull-test within 3 years</td>
<td>A3: Parkinsonism, with bradykinesia and/or asymmetric and/or levodopa responsive</td>
<td>C3: Corticobasal syndrome</td>
</tr>
</tbody>
</table>

Levels with lower numbers are considered to contribute higher certainty to a diagnosis of PSP than levels with higher numbers. Operationalized definitions of the core clinical features are provided in Table 4.
**PSP supportive features**

<table>
<thead>
<tr>
<th>TABLE 3. Supportive features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clues</td>
</tr>
<tr>
<td>CC1: Levodopa-resistance</td>
</tr>
<tr>
<td>CC2: Hypokinetic, spastic dysarthria</td>
</tr>
<tr>
<td>CC3: Dysphagia</td>
</tr>
<tr>
<td>CC4: Photophobia</td>
</tr>
</tbody>
</table>

**PSP clinical features**

- Vertical supranuclear gaze palsy
  - Slow velocity or amplitude
  - Macrosquare wave jerks on exam
  - Eyelid opening apraxia
    - Photophobia
**PSP clinical features**

- Postural instability
  - Unprovoked falls within 3 years of onset
  - Tendency to fall backwards
  - Impaired postural reflexes on testing

**PSP clinical features**

- Akinesia
  - Progressive gait freezing
  - Parkinsonism
    - Predominantly axial signs
    - Lack of tremor (usually)
    - Levodopa resistant
PSP clinical features

- Cognitive dysfunction
  - Speech language disorder
    - Non fluent variant progressive aphasia
    - Progressive apraxia of speech
  - Frontal cognitive behavioral presentation
    - Apathy
    - Bradyphrenia (slow thinking)
    - Dysexecutive syndrome
    - Impulsivity, disinhibition or perseveration

PSP clinical features

- Cognitive dysfunction
  - Corticobasal syndrome
    - Cortical signs
    - Movement disorder signs
Cortical- Basal Syndrome

Core Clinical features

- Cortical dysfunction
  - Dementia
  - Asymmetric apraxia
  - Alien limb phenomena
  - Cortical sensory loss,
  - Visual neglect

- Extrapyramidal dysfunction
  - Asymmetric parkinsonism
  - Action tremor
  - Focal limb dystonia
  - Myoclonus

Corticobasal Syndrome

Box 2. Criteria for the clinical diagnosis of corticobasal syndrome

Core features
- Insidious onset and progressive course
- No identifiable cause (e.g., tumor or infection)
- Cortical dysfunction as reflected by at least one of the following:
  - Focal or asymmetric ideomotor apraxia
  - Alien limb phenomenon
  - Cortical sensory loss
  - Visual or sensory hemineglect
  - Constructional apraxia
  - Focal or asymmetric myoclonus
  - Apraxia of speech or nonfluent aphasia
- Extrapyramidal dysfunction as reflected by at least one of the following:
  - Focal or asymmetric appendicular rigidity lacking prominent and sustained levodopa response
  - Focal or asymmetric appendicular dystonia

Supportive investigations
- Variable degrees of focal or lateralized cognitive dysfunction, with relative preservation of learning and memory, on neuropsychometric testing
- Focal or asymmetric atrophy on CT or MRI, typically maximal in parietofrontal cortex
- Focal or asymmetric hypoperfusion on single photon emission CT (SPECT) and hypometabolism on positron emission tomography (PET), typically maximal in parietofrontal cortex with or without basal ganglia with or without thalamic involvement
PSP spectrum of clinical features

Table 1. Clinical features of PSP-RS, PSP-P, PSP-PAGF, PSP-CBS, PSP-UNFA, PSP-bvFTD, PSP-C, Parkinson’s disease, and MSA-P

<table>
<thead>
<tr>
<th></th>
<th>PSP-RS</th>
<th>PSP-P</th>
<th>PSP-PAGF</th>
<th>PSP-CBS</th>
<th>PSP-UNFA</th>
<th>PSP-bvFTD</th>
<th>PSP-C</th>
<th>Parkinson’s disease</th>
<th>MSA-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigidity</td>
<td>Axial</td>
<td>Limb</td>
<td>Limb</td>
<td>axial</td>
<td>Axial</td>
<td>Limb</td>
<td>axial</td>
<td>Limb</td>
<td>Limb</td>
</tr>
<tr>
<td>Early postural instability and/or falls</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Early eye movement abnormalities</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Early cognitive decline</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Early frontal behaviour</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Non-fluent aphasias and/or apraxia of speech</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Limb dystonia</td>
<td>+</td>
<td>+</td>
<td>+/−</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+ (limb and truncal ataxia)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pyramidal and Babinski’s signs</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Levodopa response</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Dysautonomia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>


H Ling. J Mov Disorders 2016
Radiological Biomarkers for Diagnosis in PSP: Where Are We and Where Do We Need to Be?

Jennifer L. Whitwell, PhD,1,2 Günter U. Höglöf, MD,2-3 Angelo Antonini, MD,4 Yvette Bourdillon, MD, PhD,5
Adam L. Blower, MD, PhD,7 Carlo Calamardo, MD, FEAN6,7 Trudo van Elderen, MD, PhD,8 Lawrence D. Obin, MD,9
Jan Kessels, MD,10 Caygen Hui, MD,10 Irene Liban, MD,10 Alexandre Parentioli, MD,10 Olia Petranovic, MD,10
Geertje Rehaacenk, MD,10,11 Axel Rönnberg, MD,10,11 James B. Rowe, MD, PhD,10,11 Maria Stamatakis, MD, PhD,10,11
Keith A. Josephs, MD, MDT, MSc,10,11 and for the Movement Disorder Society-endorsed PSP Study Group

TABLE 3. Currently available neuroimaging biomarkers that fulfill each level of evidence in PSP

<table>
<thead>
<tr>
<th>Level</th>
<th>Utility</th>
<th>PSP-MS</th>
<th>cmPSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Research tool</td>
<td>• Basal ganglia and thalamic atrophy • DTI abnormalities in the corona radiata, lenti cerebelli, and frontal lobe tracts • Trigeminal soot in the midbrain and pons papillopathy • MR spectroscopy abnormalities • Rate of midbrain and thalamic atrophy • Resting-MTR</td>
<td>• Midbrain atrophy (PSP-S, PSP-MS, PSP-C) • Frontal atrophy (PSP-F, PSP-S, PSP-MS, PSP-C)</td>
</tr>
<tr>
<td>2</td>
<td>Supportive of clinical diagnosis</td>
<td>• Midbrain area • Midbrain area ratio • MRI • Frontal atrophy in addition to midbrain atrophy* • MRA • cSPECT</td>
<td>• Reduced basal ganglia, dentate nuclei of the cerebellum* • Reduced striatal D1/D2 receptor binding*</td>
</tr>
<tr>
<td>3</td>
<td>Supportive of pathologic diagnosis</td>
<td>• Midbrain area ratio (MMP)</td>
<td></td>
</tr>
</tbody>
</table>
Predictors of survival in PSP

- Unfavorable predictors
  - PSP-RS
  - Early onset dysphagia
  - Early onset cognitive dysfunction
  - Early falls
  - Overall disease severity score

Glasmacher et al, JNNP 2017
PSP

**Diagnostic work up**

- Clinical antemortem diagnosis!!!
- History!
- Ancillary tests
  - MRI
  - SPECT - Dopamine transporter uptake scans - DAT scan
  - Other scans investigational (Tau, Amyloid, other)

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**TABLE 2. Demographic data of the pathology confirmed cohort**

<table>
<thead>
<tr>
<th></th>
<th>PSP</th>
<th>CBD</th>
<th>MSA-P</th>
<th>PD</th>
<th>FTLD-bvFTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>204</td>
<td>54</td>
<td>51</td>
<td>53</td>
<td>73</td>
</tr>
<tr>
<td>Age at onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66.2 ± 6</td>
<td>[41-91]</td>
<td>[45-81]</td>
<td>[40-80]</td>
<td>[40-80]</td>
<td>[55-74]</td>
</tr>
<tr>
<td>Age at death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>71.8 ± 6</td>
<td>[54-54]</td>
<td>[51-60]</td>
<td>[50-60]</td>
<td>[50-60]</td>
<td>[41-64]</td>
</tr>
<tr>
<td>Disease duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.9 ± 0.3</td>
<td>[2-17]</td>
<td>[3-15]</td>
<td>[1-34]</td>
<td>[1-34]</td>
<td>[1-34]</td>
</tr>
</tbody>
</table>

Demographic data of definite PSP, CBD, MSA, PD, and FTLD patients. Data are mean ± SD (range). ANOVA followed by post hoc LSD test: *P* < 0.05, **P** < 0.01, ***P*** < 0.001, vs. PSP. Abbreviations: PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; MSA-P, multiple system atrophy with predominance of parkinsonism; FTLD, frontotemporal lobar degeneration; bvFTD, behavioral variant of frontotemporal dementia.
PSP: Clinical spectrum

Motor symptoms
- Postural instability
- Freezing of gait
- Bradykinesia
- Rigidity
- Tremor - rare
- Dysphagia
- Dystonia

Non-motor symptoms

Neuropsychiatric
- Dementia
- Depression
- Psychosis
- Anxiety
- Apathy
- Anhedonia

Autonomic dysfunction
- Bowel
- Bladder
- Sexual dysfunction

Other symptoms
- Fatigue
- Weight loss
- Weight gain (meds induced)

Sleep dysfunction
- Disrupted sleep
- Primary sleep disorders
- RLS, OSA
- Parasomnias
- Somnolence

Sensory symptoms
- Visual symptoms
- Pain

PSP management

Pharmacological

- Lack of approved PSP specific TX options
- Trial of levodopa
- Amantadine?
- Management of depression
  - SSRI s
- Management of behavioral changes
- Management of dystonia – Bot toxin
Levodopa: Side Effects

- Nausea/vomiting
- Hypotension
- Confusion
- Hallucinations
- Somnolence
- Impulse control disorders

PSP management
Non pharmacological

- Very important !!!!
- Multidisciplinary care!
PSP Affects Multiple Spheres

- Mobility
- Activities of daily living
- Sleep
- Mood and emotional well-being
- Social and family well-being
- Communication
- Cognition
Professions Involved:

- Neurology
- Clinical Nursing
- Physical Therapy, Fitness, Exercise
- Speech and Language
- Social Work
- Nutrition
- Occupational Therapy

PSP

Multidisciplinary Care Model

- Goal is to maximize the patient’s functional capacity
- Collaboration with Ability lab (RIC)
- “One stop shop approach”
Clinical Nurse

• Educates patients, e.g. about meds.
• Assists physician in pt. evaluations and procedures, e.g. Botulinum toxin.
• Follows through with making referrals to allied therapists.
• Coordinates pt.’s clinic visit to assure that all team members see pt./family.

Physical Therapist

• Teaches safety, to minimize risk of falls.
• Works on posture, balance; initiation, coordination, and range of movements.
• Does mobility training: in bed, sit-to-stand, ambulation.
• Assesses for assistive devices.
• Trains caregivers
**Occupational Therapist**

- Evaluates patient’s skills.
- Teaches adaptive techniques, e.g. for feeding, oral hygiene, dressing.
- Recommends adaptive equipment.
- Teaches how to use equipment.
- Suggests home modifications.

**Speech Therapist- for Voice and Speech**

- Evaluates individual’s speech
- Designs, carries out treatment plan to:
  - Improve speech
  - Teach compensatory strategies
  - Provide alternative methods of communication.
Speech Therapist-
for Dysphagia

- Performs swallow screening.
- Teaches compensatory techniques.
- Makes referral to nutritionist for diet modifications.
- Makes referral for PEG if appropriate

Nutritionist

- Recommends balanced food guide.
- Recommends diet modifications as necessary.
- Understands if/when protein is a factor in medication absorption.
- Understands role of vitamins, supplements, herbs.
**Social Worker**

- Assesses patient and family functioning.
- Counsels patient, care partner, family.
- Leads support groups for patients and caregivers.
- Provides info about concrete services.
- Accesses, and coordinates care with, community programs and agencies.
- Plans, conducts educational programs.

**Social Worker
Scope of Services**

Referrals and information re:
- Legal disability & guardianship counsel
- Transportation assistance programs
- Home care and long-term care
- Patient and family counseling
- End of life counseling
Palliative care

- Palliative care physician
- Social worker
- Spiritual counsel
- Team
- Goal to empower the patient to make right decisions at every stage of disease!

Multidisciplinary Care for Patients and Families

- Holistic approach to a complex disease
- Through ongoing team communication, treatment changes as patient changes:
  - “One size does not fit all.”
PSP
The horizon is optimistic !!!

Management of PSP

Treat the whole spectrum of disability !!!
A lot of challenges BUT the horizon is optimistic !!