

HSCP Study Day, RCP, London  
 PSP Association  
 25 October 2018



## PSP: Early Diagnostic Clues & Management



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 Queen Square Brain Bank  
 UCL Institute of Neurology




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Historical Brief

An Early Photographic Case of Probable Progressive  
 Supranuclear Palsy



**'An air of singular majesty'**



1889

Goetz. MDJ. 1996

**'A Man'**

Cornelis Anthonisz  
 (Netherland)



1530

LeWitt. Lancet Neurol. 2017

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### Steele, Richardson & Olszewski 1964



- 9 cases –  
 Progressive neurodegenerative condition:**
- Vertical supranuclear gaze palsy
  - Pseudobulbar palsy
  - Dysarthria
  - Axial rigidity
  - Retrocollis
  - Mild cognitive impairment

Steele, Richardson, Olszewski, Arch Neurol 1964

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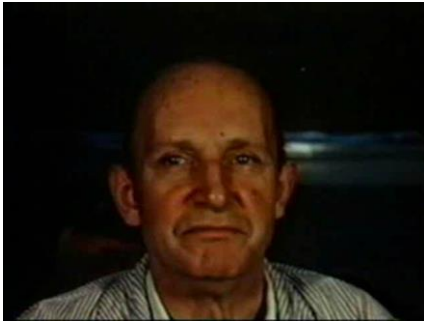
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**Steele, Richardson & Olszewski 1964**



**Patient 1**



Steele, Richardson, Olszewski, Arch Neurol 1964

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**UCL**

**Different Types of PSP**

1964	PSP-Richardson's syndrome (PSP-RS)	50%
2005	PSP-Parkinsonism (PSP-P)	30%
2007	PSP-Pure akinesia with gait freezing (PSP-PAGF)	5-10%
2005	PSP-Corticobasal syndrome (PSP-CBS)	<5%
2006	PSP-Primary non-fluent aphasia (PSP-PNFA)	<5%
2010	PSP-Frontotemporal dementia behavioural variant (PSP-FTDbv)	<5%

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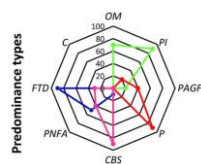
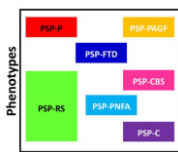
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**UCL**

**RESEARCH ARTICLE**

**The Phenotypic Spectrum of Progressive Supranuclear Palsy: A Retrospective Multicenter Study of 100 Definite Cases**

Gesine Raspoedek, MD,<sup>1,2,3\*</sup> Mario Stamelou, MD,<sup>1,4\*</sup> Carolin Kurz, MD,<sup>1,2</sup> Leslie W. Ferguson, MD,<sup>5</sup>  
 Alexander Flanagan, MD,<sup>6</sup> Wan Zheng Ouy, MD,<sup>6</sup> John C. van Swieten, MD,<sup>7</sup> Claire Troakes, PhD,<sup>7</sup>  
 Safa al Sarraj, FRCPsych,<sup>1</sup> Eleni Gatsi, MD,<sup>8</sup> Charles Gao, MD,<sup>8</sup> Eduardo Tolosa, MD,<sup>9</sup>  
 Wolfgang H. Oertel, MD,<sup>3</sup> Armin Giese, MD,<sup>10</sup> Sigurd Roesler, MD,<sup>10</sup> Thomas Arzberger, MD,<sup>10</sup>  
 Stefan Waagstein,<sup>11,12</sup> and Ginter U. Hoglinger, MD,<sup>13,14</sup>  
 for the Movement Disorder Society—endorsed PSP Study Group



MDJ 2014

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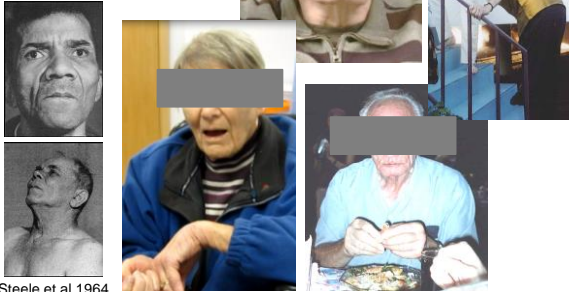
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'Fixed staring gaze'  
 'Mona Lisa fixity of gaze'  
 'Procerus sign'  
 'Dirty tie syndrome'



Steele et al 1964

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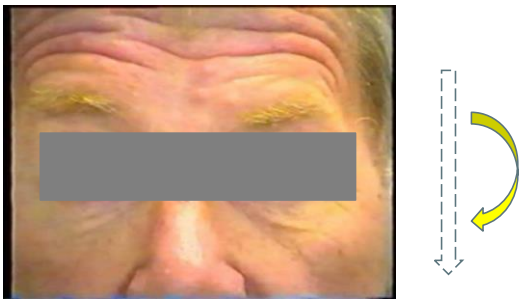
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**Eye signs in early PSP:**  
 'Round the houses' sign & slow vertical saccades



N Quinn. Ann Neurol 1996

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**Classic presentation of PSP -**  
**Richardson's Syndrome (PSP-RS)**



- Signs supportive of RS:**
- Square wave jerks
  - Hypometric pursuit
  - Restricted downgaze
  - Slow vertical saccades
  - Fast small finger tapping
  - Growling speech with hypophonia
  - Applause sign (4 claps)
  - Fast micrographia
  - Unsteady gait with upright posture

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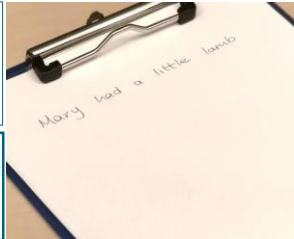
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### Fast Micrographia in PSP

**A** PD-OFF handwriting  
 Mary had a little lamb its fleece was white as snow  
 Mary had a little lamb its fleece was white as snow  
 Mary had a little lamb its fleece was white as snow  
 Mary had a little lamb its fleece was white as snow



**'Microscopic' handwriting in PSP**  
 Mary had a little lamb its fleece was white as snow  
 Mary had a little lamb its fleece was white as snow  
 Mary had a little lamb its fleece was white as snow  
 Mary had a little lamb its fleece was white as snow

Ling et al. Brain 2012

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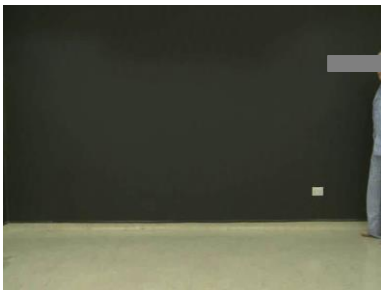
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### Gait in PSP

*'Drunken sailor', 'Dancing bear', 'Gunslinger' gait*




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### Impulsive motor recklessness in PSP often lead to falls and injuries

PSP - 'Rocket sign'

Parkinson's Disease




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**PSP-PAGF: Gait Ignition Failure and Freezing of Gait in PSP**

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**Postural instability, Spontaneous Falls  
Gait Freezing, Motor Recklessness**




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**Different Types of PSP**

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### PSP-PPA: Primary progressive aphasia

#### The 'Vicar of Dibley' Sign

No...no...no...no...no...YES

**Binary reversal error**  
Said 'yes' and nodded head but meant 'no' with self-awareness of error



Courtesy of Professor Nick Fox

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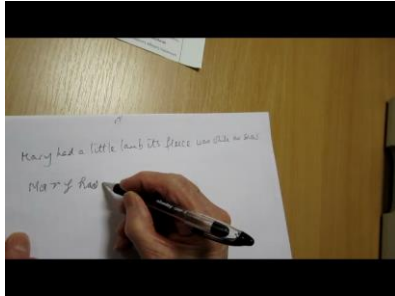
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### An 82-year-old man presenting with a 2-year history of progressive difficulties 'getting the words out' and writing

Apraxia of speech

Agraphia (Apraxia + Language impairment)



PSP-CBS

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### PSP-CBS: 'Clumsy hand'



Limb apraxia



Orobuccal apraxia

Ling et al. Characteristics of PSP-CBS. NAN 2014  
Ling et al. Is it useful to classify PSP and CBD as different disorders? Yes. MDCP 2018  
Hoglinger et al. Is it useful to classify PSP and CBD as different disorders? No. MDCP 2018

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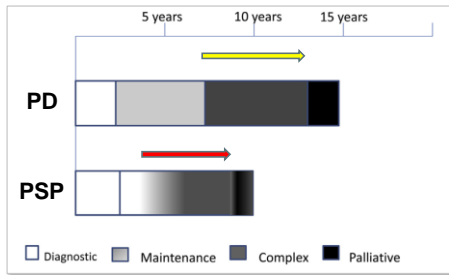
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**Significant morbidity for extended period of time  
=> Mainstay of treatment is improvement of quality of life**



Wiblin et al. PRD. 2017

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**Disease-modifying treatment has NOT been shown to be effective**

Treatment	Class	Mechanism	Participants	Trials
<b>Davunetide</b>	Growth factor neuropeptide	Decrease tau phosphorylation to promote microtubule stability	PSP: N=313	Boxer et al. 2014
<b>Tideglusib</b>	Glycogen synthase kinase-3 (GSK-3) inhibitor	Inhibitor of tau hyperphosphorylation	PSP: N=146	Tolosa et al. 2014
<b>Lithium</b>	GSK-3 inhibitor	Inhibitor of tau hyperphosphorylation	AD: N=71	Hampel et al. 2009
<b>Riluzole</b>	Neuroprotective agent	Block CNS glutamatergic neurotransmission	PSP & MSA: N=767	Bensimon et al. 2009 (NNIPPS)

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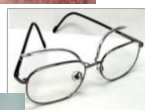
**Visual Symptoms in PSP**

- 'I don't mean to appear rude'* (staring gaze)
- 'I'm really not crying'* (Light sensitivity)
- 'I'm not really asleep'* (Involuntary eye closure)



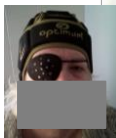
**Other symptoms:**

- Dry sore eyes
- Corneal ulcers
- Double vision
- Difficulties scanning books and reading



**Managements:**

- Botulinum toxin injection
- Prism glasses
- Wrap-around sunglasses
- Audio books
- Artificial tear drops
- Lundie loops




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## Acetylcholinesterase Inhibitor

**Side Effects (mobility, ADL)**

**Outweigh Benefits (Cognition, behaviour)**

- Donepezil (NOT recommended)

**PSP:** Improve cognition but deterioration in ADL & mobility

**FTD:** No improvement in cognition, worsens behaviour

- Galantamine (NOT recommended)

**bvFTD, PPA:** No improvement in behaviour or language

- Rivastigmine (Inconclusive, off-label use)

**bvFTD, PPA:** Improve behavioural symptoms and caregiver burden, but NOT cognition

Karakaya 2012, Mendez 2007, Manoochemhri 2012, Kerchner 2011  
Kertesz 2008, Moretti 2004, Moretti 2004

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## UCL

ORIGINAL ARTICLE

### Sleepless Night and Day, the Plight of Progressive Supranuclear Palsy

Christine M. Walsh, PhD<sup>1</sup>, Leslie Ruoff, BS RPSGT<sup>1</sup>, Kathleen Walker, BA<sup>1</sup>, Aislinn Emery, BS<sup>1,2</sup>, Jonathan Verbel, BA, RPSGT<sup>1</sup>, Eleonora Karageorgiou, MD, PhD<sup>1,3</sup>, Phi N. Luong, BS<sup>1</sup>, Indira Manooch, PhD<sup>1</sup>, Hilary W. Heuer, PhD<sup>1</sup>, Adam L. Boer, MD, PhD<sup>1</sup>, Lea T. Grinberg, MD, PhD<sup>1,4</sup>, Joel H. Kramer, PsyD<sup>1,5</sup>, Bruce L. Miller, MD<sup>1</sup>, Thomas C. Neylan, MD<sup>2,6</sup>

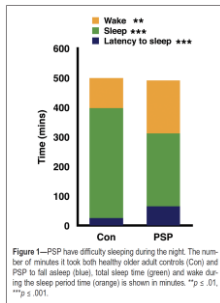


Figure 1—PSP have difficulty sleeping during the night. The number of minutes it took both healthy older adult controls (Con) and PSP to fall asleep (blue), total sleep time (green) and wake during the sleep period time (orange) is shown in minutes. \*p < .05, \*\*p < .01.

Sleep. 2017

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## Zopiclone



- GABA Agonist
- 5-10mg/day

⇒ Improve speech, swallowing, hypersalivation  
⇒ Improve motor function (bradykinesia, rigidity, dexterity)

- Side effects:  
Respiratory depression, sleep apnoea, fatigue, confusion, drowsiness, dizziness, postural hypotension

Daniele et al. Zopiclone in PSP. NEJM. 1999  
Chang et al. Case report. 2014  
Cotter et al. 2010

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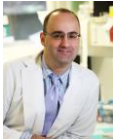
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**PSP / CBD Multidisciplinary Clinic  
Queen Square National Hospital**



**Professor  
Andrew Lees**

Neurologists  
Palliative care consultant  
Swallowing & speech therapist  
Physiotherapist  
Dietician  
Clinical psychologist  
PSP Association care adviser  
Research team & Brain Donation Nurse



**Professor  
Huw Morris**



**Karen Green  
Dietician**

**Tricia Gilpin  
SALT**

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**UCL**

**PSP/CBD Audit:  
Evaluation of care provision (2018)**

**Data analysis:**  
Helen Ling

**Audit leads:**  
Helen Ling  
Helen Grote

**Advisor:**  
Huw Morris

**Department:**  
Movement Disorders  
National Hospital for Neurology and Neurosurgery  
Queen Square Institute of Neurology

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**UCL**

**PSP/CBD Audit:  
Evaluation of care provision (2018)**

**Aims:**

- N = 50
- Assess care provision in out-patient clinics
- **Multidisciplinary clinic**  
Vs. **Non-MDT specialist clinics:**  
General neurology clinic  
Dementia clinic  
Movement disorders clinic

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**Ten key standards of care at specialist clinics:**

- 1. Promptly assessed within 2 months of referral
- 2. Follow up at least every 6 months
- 3. Provided Information about PSP Association
- 4. Dietician input (nutrition, supplement, weight changes)
- 5. Access to swallowing and language therapy
- 6. Access to physiotherapy
- 7. Assessment of mobility at home
- 8. Access to occupational therapy
- 9. Access to palliative care
- 10. Assessment of visual symptoms

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**PSP/CBD MDT clinic performs better in the following outcome measures (in red):**

- 1. Promptly assessed within 2 months of referral
- 2. Follow up at least every 6 months
- 3. Provided Information about PSP Association
- 4. Dietician input (nutrition, supplement, weight changes)
- 5. Access to swallowing and language therapy
- 6. Access to physiotherapy
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**Thank you!**

**Helen Ling**

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