Progressive Supranuclear Palsy (PSP) and the Corticobasal Syndrome (CBS)

Dr Luca Passamonti
lp337@medschl.cam.ac.uk
Getting the right diagnosis

For the patient
For the carers and family
For you the neurologist/physician
PSP – its not Parkinson’s disease!

Often called a ‘Parkinson-plus’ syndrome, but it is not like PD

Often called “atypical parkinsonism”

Typical rheumatoid arthritis is not atypical-osteoarthiritis
Typical trigeminal neuralgia is not atypical-migraine.
Typical corticobasal syndrome is not atypical
Typical PSP is not atypical
## PSP versus PD

<table>
<thead>
<tr>
<th></th>
<th>PSP</th>
<th>PD</th>
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<tbody>
<tr>
<td><strong>Symmetrical</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Rigidity</strong></td>
<td>axial</td>
<td>limb</td>
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<tr>
<td><strong>Akinesia</strong></td>
<td>Severe, global</td>
<td>Mild to moderate</td>
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<tr>
<td></td>
<td>Even in loose limbs</td>
<td></td>
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<tr>
<td><strong>Tremor</strong></td>
<td>No</td>
<td>Yes</td>
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<tr>
<td><strong>Falls</strong></td>
<td>Early, spontaneous</td>
<td>Late, with freezing</td>
</tr>
<tr>
<td><strong>Eyes</strong></td>
<td>Vertical paresis</td>
<td>‘normal’</td>
</tr>
<tr>
<td><strong>Voice</strong></td>
<td>Dysarthrophonia, distorted, volume control</td>
<td>Hypophonia Quiet</td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td>Marked early changes</td>
<td>Later dementia</td>
</tr>
<tr>
<td></td>
<td>Loss of fluency</td>
<td></td>
</tr>
<tr>
<td><strong>Levodopa</strong></td>
<td>Poor response</td>
<td>Very good response</td>
</tr>
<tr>
<td><strong>Gait</strong></td>
<td>Head up, sniffing the air, Leaning back</td>
<td>Head down, stooped, leaning forward</td>
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<tr>
<td><strong>Looks like PD?</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
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New PSP criteria
Hoeglinger et al, Mov Disord 2017

“Classical PSP” = PSP-Richardson’s syndrome, PSP-RS,
(cf. Steele, Richardson & Olszewski 1964, Litvan 1996)

Clinically probable PSP-RS if

1. sporadic, progressive, onset >40 years
2. vertical gaze palsy (restriction OR slowing)
3. unprovoked falls or tendency to falls (<3 years)

→ highly specific (true negative rate), not very sensitive (true positive rate), ideal for clinical trials
What symptoms predict PSP
vs CBD, MSA, PD, bvFTD
Respondek et al Mov Dis 2017

- Supranuclear gaze palsy – especially <3 years
- Postural instability – especially <1 year, <3 years
- Akinetic rigidity if axial and levodopa resistant

- Non-fluent <3 years (differential FTD/PPA)
- Dysarthria, dysphagia < 3 years
PSP family of phenotypes

- PSP-GF (gait freezing)
- PSP-P (parkinsonism)
- PSP-F (Frontal)
- PSP-SL (speech/language)
- PSP-CBS (corticobasal)
PiPPIN: Pick’s disease and Progressive Supranuclear Palsy prevalence and incidence study

100 cases of PSP and CBD in 2 years, from 1.6m people (=4000 in the UK)

(Coyle-Gilchrist et al, 2016)
Survival

From onset to median death 5-7 years
From onset to diagnosis ~3 years

Dell’Aquila et al 2013
But all major US and European studies similar
Cognitive profile of PSP – early, challenging, distressing

In classical PSP-Richardson’s syndrome:

- Apathy, impaired abstract thought, poor verbal fluency,
- utilisation behaviour, frontal release signs,
- (also - irritable, selfish, stubborn, rigid …)

But in the “PSP family” of syndromes you also find:

PSP-SL: speech and language, cf. PNFA, dynamic aphasia
PSP-F: ‘frontal’ overlap with frontotemporal dementia
Quick bedside test = Verbal fluency

Seven P-words/minute
~95% accurate to distinguish PD from PSP

Rittman et al. JNNP 2012
Impulsivity - physical and mental

Cramming food
   Even while choking

Cannot tolerate delay
   Stand – walk - fall

Cant suppress a habitual response
Apathy: Common – frustrating – harmful

It’s about motivation and effort

It is not Depression
  Most PSP patients will say that they feel well
  Low mood is not common

It is not Akinesia/bradykinesia
  But can look like it.

A strong predictor of survival

Lansdall et al, Brain 2017
Tau in PSP

Thanks to Dr Kieran Allinson
Cambridge Brain Bank
AV1451 “Tau” PET early in PSP
Passamonti et al Brain 2017

→ For clinical trials to test “anti-tau” treatments that prevent spread or enhance clearance of tau
Corticobasal syndrome (=clinical disorder) & Corticobasal degeneration (=neuropathology)

“Classical CBS”:

1. Progressive and Asymmetric
2. higher cortical functions – apraxia, cortical sensory loss, alien limb
   also non-fluent aphasia, loss of grammar, visuospatial deficits
3. Movement disorder – dystonia, focal myoclonus, akinetic-rigidity
   +/- mirror movements
Alien limb

Levitation
Face touching
Interference
Complex tasks
Not delusions of control
Neuroimaging in Corticobasal Syndrome

MRI: NHS: Global atrophy (mild) and lateralised parietal atrophy (common)
SPECT: asymmetric parietal hypometabolism (+occipital, +frontal, +temporal)
PSP and CBD Summary

Common but not Parkinson’s!

Clinical diagnosis (imaging support)

Characteristic signs
Management of PSP and CBS

Diagnosis
Engagement and Information
Autonomy and Control
Treat proactively
Harm avoidance
A Guide to Cognition for Health and Social Care Professionals

Pathway of Care for PSP
A guide for Health and Social Care Professionals

Best Practice in PSP

Early Stage (including diagnosis)

IN BRIEF...
Able to walk but falls occasionally; difficulty reading due to gaze; mild vocal changes such as quietening; some changes in mood and reduced levels of social interaction. (see reverse for symptoms)

Aims
To ensure that people with PSP and their families are:
- Given a prompt and accurate diagnosis (including 'possible' and 'probable')
- Well supported at, during and after diagnosis, including in coming to terms with condition
- Clearly directed to information and support
- Given details of an identified key worker to support ongoing information and services
- Assisted to develop awareness, and supported to adapt to the changes of PSP
- Helped to manage and reduce any symptoms
- Assisted in maximising independence and participation in everyday life

Key Considerations
PSP is often misdiagnosed. Prompt referral for assessment by a movement disorder specialist is advised.

http://www.pspassociation.org.uk/
Autonomy and Control

Most patients retain mental capacity

Communication is slow and difficult
  But that’s our problem, not the patients
Symptomatic Treatments 1 - Motor

Akinetic-rigidity:
  Sinemet/madopar – rapid escalation, taper if ineffective
    1. Poor response does not mean no response
    2. A partial response for 1-3 years is worth it
    3. Levodopa does not cause dyskinesia in PSP (it is not PD after all)

  Amantadine – for motor symptoms and non-motor
    ~50% some response, variable, esp. young mild cases

Pain/dystonia/retrocollis
  **botox** injection eg. paraspinal muscles, finger flexors

Lid apraxia and blepharospasm – **Botox** –
Myoclonus – **clonazepam** or **levitiracetam** good,
  avoid valproate
Symptomatic Treatments 2 – Mood

Depression (don’t make assumptions about mood)
SSRIs – **citalopram** (liquid via peg or if dysphagic)
**mirtazepine** – appetite and weight gain useful
Avoid tricyclics (amitritylline) - side effects, drowsy, falls

Emotional incontinence – low dose citalopram (SSRI)
Symptomatic Treatments 3 - other

Urology or Neurology –
non-drug treatments mainstay
drugs – 5HT3 (Mirabegron) rather than ACh (oxybutynin) and desmopressin

Sleep
address root causes, anxiety, pain, sleep-hygiene etc
*Treat bladder dysfunction*
Low dose benzodiazepines, zolpidem, melatonin,

Amnesia (CBD) cholinesterase inhibitors (often AD)
Functional blindness (CBD) ophthalmology review, (CBD) register as sight impaired
Symptomatic Treatments 5

Cognitive and personality change

inclusive of family & carers
personalised
mainly non-pharmacological

consider SSRI/Trazodone
Symptomatic Treatments 6 – psychosis

• Psychosis
  – rule out infection, infection or infection
  – look to your medications – amantadine, cholinergics, opioids
  – question the diagnosis (DLB?, C9orf72-FTD?)
Harm avoidance

• Catastrophic harm from neuroleptics
  – Severe, irreversible, unnecessary
  – Haloperidol >> risperidone >> quetiapine

• Moderate risk
  – Cholinergics for bladder
  – Tricyclics for mood
  – Opiates for pain
  – …..
Multidisciplinary Team

Palliative care
Occupational Therapy
Physiotherapy
Speech and Language therapy
Independent living team
The future of treatment

Disease modifying therapy
Disabling Syndrome

Mild signs

Atrophy

Connection breakdown

‘Junk’ proteins
PSP & CBS “lifespan”

- TAU
- Connection breakdown
- Atrophy
- Mild signs
- Disabling Syndrome

Aggregate
Toxic fibrils
Sticky
Disease modifying therapy

- Clearance
- Cell to cell spread in the brain
- Aggregate
- Toxic fibrils
- Sticky
- Cell death
- Tolerance
Disease modifying therapy

Clearance

Cell to cell spread in the brain

Cell death

Tolerance

UPR Inhibitors
(Trazodone?)

Aggregation

Bristol-Myers Squibb

Abbvie

Toxic fibrils

Sticky
But – how to know if a drug is working?

“Mock trials” and preparatory observational studies

PROSPECT-UK

A UK Registry and Longitudinal Cohort for PSP/CBS

PROSPECT-M-UK

- Funded by the PSP Association and MSA Trust
- Study of PSP/CBD/MSA/Atypical Parkinsonism and controls
- Longitudinal biomarker study
  - 7 UK centres
- Cross-sectional study
  - UK wide – remote access
Summary

• Active Treatment for PSP and CBS symptoms
  – rewarding but multifaceted
  – In the context of a MDT

• Clinical Trials imminent, to arrest progression