CORTICOBASAL SYNDROME, CORTICOBASAL DEGENERATION, AND PROGRESSIVE SUPRANUCLEAR PALSY:
WHAT ARE THE TAUOPATHIES?

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TAUOPATHIES

CBD

FTLD

PSP
MANY DISEASE ARE TAUOPATHIES

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Anatomy (major areas affected in typical cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4R TAUOPATHIES</td>
<td></td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>Cortex and basal ganglia</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Basal ganglia, brainstem and cerebellum</td>
</tr>
<tr>
<td>FTDP-17 T</td>
<td>Cortex, basal ganglia and brainstem</td>
</tr>
<tr>
<td>3R TAUOPATHIES</td>
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<tr>
<td>Pick’s disease</td>
<td>Cortex and limbic lobe</td>
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<td>FTDP-17 T</td>
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<tr>
<td>3R + 4R TAUOPATHIES</td>
<td></td>
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<tr>
<td>Alzheimer disease</td>
<td>Cortex and limbic lobe</td>
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<tr>
<td>FTDP-17 T</td>
<td>Cortex and limbic lobe</td>
</tr>
</tbody>
</table>

Dickson et al. (2011) *J Mol Neurosci* 45:384-389
PSP CLINICAL FEATURES

• Behavior:
  – Apathy, obsessive/compulsive behaviors, utilization

• Cognitive profile: executive dysfunction

• Motor:
  – Parkinsonism: axial rigidity, postural instability, bradykinesia, reduced blink
  – Supranuclear gaze palsy
  – Dysphagia/dysarthria

Romano & Colosimo
Neurology 2001
PSP CRITERIA UPDATED THIS YEAR

- Sporadic occurrence
- Age 40 or older at onset
- Gradual progression of PSP-related symptom
- Core features:
  - Oculomotor dysfunction
  - Postural Instability
  - Akinesia
  - Cognitive dysfunction
<table>
<thead>
<tr>
<th>Certainty</th>
<th>Oculomotor</th>
<th>Postural Instability</th>
<th>Akinesia</th>
<th>Cognitive Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>O1: 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 (nf/agrammatic PPA or AOS)</td>
</tr>
<tr>
<td>Level 2</td>
<td>O2: Slow velocity of vertical saccades</td>
<td>P2: Tendency to fall on the pull-test within 3 years</td>
<td>A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant</td>
<td>C2: Frontal cognitive/behavioral presentation</td>
</tr>
<tr>
<td>Level 3</td>
<td>O3: Frequent macro square wave jerks or apraxia</td>
<td>P3: More than two steps backward on the pull-test within 3 years</td>
<td>A3: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive</td>
<td>C3: Corticobasal syndrome</td>
</tr>
</tbody>
</table>
SOME VARIANTS ARE MORE LIKELY TO

Clinical syndrome

Richardson’s syndrome —> PSP-RS —> RS not due to PSP

Parkinsonism —> PSP-P

Gait freezing —> PSP-PGF

Corticobasal syndrome —> PSP-CBS

nfvPPA —> PSP-SL

bvFTD —> PSP-F

Cerebellar ataxia —> PSP-C

PSP pathology

PSP with mixed pathology

Other pathology

Boxer et al. Lancet Neurol
PSP-RICHARDSON SYNDROME

- Unexplained falls, Unsteady gait, Bradykinesia
- Personality changes (apathy, disinhibition)
- Cognitive slowing, Executive dysfunction
- Slow, ataxic, spastic, and hypophonic speech, Dysphagia
- Impaired eye movement (slow vertical saccades, apraxia eyelid opening)
- Vertical supranuclear gaze palsy
  - Onset variable (might not present until 3–4 years after)
  - Decreased velocity, amplitude of vertical > horizontal saccadic
  - Decreased / absent optokinetic nystagmus
• Variable combo of:
  – Progressive limb rigidity
  – Apraxia
  – Cortical sensory loss
  – Alien limb
  – Bradykinesia
  – Unresponsive to levodopa
PSP-SPEECH/LANGUAGE

- nfvPPA
- Agrammatism
- Effortful, halting speech with inconsistent speech sound errors and distortions (AOS)
STN ATROPHY
ATROPHY OF CEREBELLAR DENTATE NUCLEUS
PSP PATHOLOGY

• Neuronal loss and gliosis

• Hyperphosphorylated MAPT accumulation
  – Glial tauopathy:
    • tufted astrocytes

CORTICOBASAL SYNDROME: MULTIPLE PATHOLOGIES

- Dystonia, Parkinsonism, apraxia, cortical sensory loss, loss of voluntary limb control
- Syndrome now associated with several pathologies:
  - CBD
  - PSP
  - DLB
  - AD
  - FTLD-TDP43
  - Prion disease
CORTICOBASAL DEGENERATION: MULTIPLE CLINICAL PRESENTATIONS

• Different presenting syndromes can have CBD pathology:
  – Behavioral syndrome (FTD)
  – Non-fluent aphasia syndrome
  – PSP syndrome
  – CBS
Syndrom

CBS

PSP

FTD

Non-fluent PPA

Pathology

CBD

PSP

DLB

AD

TDP-43

Prion
# PROPOSED CLINICAL PHENOTYPES OF CBD

<table>
<thead>
<tr>
<th>Probable CBS</th>
<th>Asymmetric presentation of 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 2 of: d) orobuccal or limb apraxia, e) cortical</th>
</tr>
</thead>
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<tr>
<td>FBSS</td>
<td>Two of: a) executive dysfunction, b) behavioral or personality changes, c) visuospatial deficits</td>
</tr>
<tr>
<td>PSPS</td>
<td>Three of: a) axial or symmetric limb rigidity or akinesia, b) postural instability or falls, c) urinary incontinence, d) behavioral changes, e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades</td>
</tr>
</tbody>
</table>

Armstrong et al. *Neurology*, 2013
PATIENT 1

58 RH F 1 year Left sided clumsiness

• Difficulty descending stairs: hold railing with RUE

• 6 months later difficulty with sequence of starting car

• Handwriting worse, tremor b/l
PATIENT 1

• Exam
  – Praxis worse L
  – Tone increased, cogwheel
  – Coordination worse on left, slow

• Cognitive testing:
  – Pretty good overall with minor problems in calculations and copying, but impaired phonemic fluency
TYPICAL FDG PET AND MRI PATTERNS

Sha et al. *Alz Res & Ther* 2015
PATIENT 2

70 M 1.5 years of progressive motor and cognitive changes

• Skiing accident with concussion
• R haŶ’d ĐoordiŶatioŶ prodleŵs: ĐaŶ’ t write,
  ĐaŶ’ t eat
• Speech slow and slurred
• Memory problems, difficulty with details, planning

Exam:
• Memory loss recall 1/5, names 4 F words
• Eye movements with overshoot, saccadic
• Slurred speech and slow
• Right hand dystonic with increased tone
  RUE, RLE
AMYLOID PET IS SUGGESTIVE OF AD PATHOLOGY
CBS-PIB⁻ < NC

CBS-PIB⁺ < NC

CBS-PIB⁻ < CBS-PIB⁺

CBS-PIB⁺ < CBS-PIB⁻

Sha et al. *Alz Res & Ther*
CORTICOBASAL DEGENERATION

• Macroscopic Pathology
  – Narrowing of cortical gyri especially frontal; pre- and postcentral gyri atrophic to varying degrees; atrophy is often asymmetric
  – May be flattening of caudate nucleus; brown discoloration of globus pallidus
  – Loss of neuromelanin pigment in the substantia nigra with better pigmentation in locus ceruleus
  – Subthalamic nucleus (STN) usually preserved
FTLD-MAPT (CBD)

- Abundant swollen cortical neurons
- Glial Tauopathy:
  - Coiled bodies
  - Astrocytic plaques

CONCLUSIONS

• PSP and CBD can have different clinical presentations
• PSP-RS is the most common and most predicts PSP pathology
• CBS usually indicates CBD but can have alternate pathologies
STANFORD ADRC

• Free exercise and wellness classes (Yoga, Tai Chi, Dance, Qi Gong)
• Free support services (caregiver workshops, support groups, classes)
• Travel reimbursement, participation incentives, and feedback to share with your family and health care provider
• Stanford Neuroscience Supportive Care Program: www.stanfordhealthcare.org/nscp

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https://med.stanford.edu/adrc.html
Thank you!
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