Cognitive and Behavioral Issues in PSP, CBD, FTD, and PPA

Bradley F. Boeve, M.D.

Division of Behavioral Neurology
Department of Neurology
Mayo Clinic
Rochester, Minnesota

Alzheimer’s Disease Research Center
Mayo Foundation
Cognitive and Behavioral Issues in PSP, CBD, FTD, and PPA

Outline

• History
• Brain-Behavior Correlations
• The Syndromes/Disorders
• Management
• Resources
• Questions
History
PSP, CBD, FTD, and PPA

History

• PSP – initially characterized in the 1960s

• CBD – initially characterized in the late 1960s

• PPA – initially characterized in 1982
  – nonfluent variant
  – semantic variant

• FTD – initially characterized in 1994
PSP, CBD, FTD, and PPA

History

- The 4 different disorders have been classically considered to be distinct and separate.

- Growing evidence that these are strikingly similar, with one of the primary distinctions being what parts of the brain are maximally affected.
Brain-Behavior Correlations
PSP, CBD, FTD, and PPA
Brain-Behavior Correlations

Templates

A B C
PSP, CBD, FTD, and PPA
Brain-Behavior Correlations

Thinking/Cognitive

Behavior

Language
PSP, CBD, FTD, and PPA
Brain-Behavior Correlations

Memory - hippocampi
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Brain-Behavior Correlations

“Emotional valence”
- amygdala
Problem-solving, reasoning, complex decision-making - dorsolateral frontal regions
Socially appropriate behavior, “theory of mind” - ventromedial frontal regions
Motivation, spontaneous actions - anterior cingulate region

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Brain-Behavior Correlations
Language - left frontal, temporal, parietal regions

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Brain-Behavior Correlations
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Brain-Behavior Correlations

**Prosody** - right frontal, temporal, parietal regions
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**Brain-Behavior Correlations**

- **Visual recognition** - right > left temporal and occipital regions

[Diagram showing brain regions labeled A, B, C with visual recognition areas marked.]
Social disinhibition
Loss of empathy and insight
Change in food preferences
Hoardling of food
Utilization behavior
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Brain-Behavior Correlations

Memory loss
Executive dysfunction

Poor planning and judgement

Inability to multitask
Loss of motivation

Tendency to sit, not initiative conversations or actions

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Brain-Behavior Correlations
PSP, CBD, FTD, and PPA
Brain-Behavior Correlations

- Poor verbal expression
- Poor naming of objects and people

Brain-Behavior Correlations

A

B

C

“Speech”

Naming
Aprosodia

Monotone voice

Unable to interpret inflections in voice another person’s voice
Visual agnosia
Unable to recognize objects and people
The Syndromes/Disorders
Progressive Supranuclear Palsy
Clinical Features

- symmetric rigidity and bradykinesia
  - axial > appendicular
  - levodopa unresponsive

- postural/gait instability
  - frequent falls

- extraocular movement dysfunction
  - saccadic pursuits
  - delayed, slowed saccades
  - supranuclear gaze palsy, particularly downgaze

- apathy, bradyphrenia
Corticobasal Syndrome/Corticobasal Degeneration
Clinical Features

- Progressive course
- Asymmetric findings
- Limb rigidity
- Limb apraxia

Progressive asymmetric rigidity and apraxia
Behavioral Variant Frontotemporal Dementia

Clinical Features

- personality/behavioral changes
- loss of empathy/sympathy
- loss of insight
- apathy
- social disinhibition
- change in food preferences
- poor judgement and planning
Primary Progressive Aphasia
Clinical Features

- **Nonfluent**
  - changes in speech/language production

- **Semantic**
  - loss of nouns and word meaning
Frontotemporal Lobar Degenerations

- PSP
- CBD
- FTD
- PPA
Management
PSP, CBD, FTD, and PPA
Management

**Pharmacotherapy**
- Improve symptoms
- Manage behaviors
- Decrease injury risk

**Non-Pharmacotherapy**
- Improve symptoms
- Manage behaviors
- Decrease injury risk
- Improve caregiving strategies

*Improve QOL for all involved*
PSP, CBD, FTD, and PPA
Management

• Approach – ask patients and caregivers to list and then rank which symptoms/problems are most bothersome, which allows the clinicians to tailor the management plan.

• Problem list:
  – Cognitive
  – Neuropsychiatric
  – Motor
  – Speech/swallowing
  – Sleep
PSP, CBD, FTD, and PPA Management

• There are no FTD-approved medications specifically developed to impact PPA, CBD, FTD, and PPA

• There are few well-designed studies that have shown that any medication improves symptoms in any of these disorders

• There is considerable debate among clinicians whether any medications are worth using in patients with any of these disorders

• Almost all medications to be discussed are expensive and are associated with mild to severe side-effects
PSP, CBD, FTD, and PPA
Management

Cognitive

Education/Counseling/Behavioral Management:

Stay physically, mentally, and socially active

Establish and maintain a daily routine

Religious use of a daily planner
Cognitive (cont.)

Executive dysfunction, memory impairment:

? Carbidopa/levodopa, dopamine agonists
  Sinemet®, Mirapex®, Requip®

? Cholinesterase inhibitors
  Aricept®, Exelon®, Razadyne®

? Psychostimulants
  Provigil®, Nuvigil®, Ritalin®, Adderall®, Desoxyn®

? NMDA antagonists
  Namenda®
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Management

Neuropsychiatric

Education/Counseling/Behavioral Management:

Develop tolerance and choose your battles!

Acknowledge and redirect; refrain from arguing

“Employ therapeutic fibs”

Support group involvement

Work with local psychologists and psychiatrists
Neuropsychiatric (cont.)

Disinhibition, socially inappropriate behavior, delusions:

? Selective serotonin reuptake inhibitors
  *Celexa®, Lexapro®, Paxil®, Prozac®, Remeron®, Zoloft®*

? Atypical neuroleptics
  *Seroquel®, Respirdal®, Zyprexa®*

? Anticonvulsants
  *Depakote®, Neuronin®, Tegretol®*

? Beta-blockers
  *Inderal®*
Apathy:

- **Selective serotonin reuptake inhibitors**
  - Celexa®, Lexapro®, Paxil®, Prozac®, Zoloft®

- **Psychostimulants**
  - Provigil®, Nuvigil®, Ritalin®, Adderall®, Desoxyn®

- **Carbidopa/levodopa, dopamine agonists**
  - Sinemet®, Mirapex®, Requip®

- **Cholinesterase inhibitors**
  - Aricept®, Exelon®, Razadyne®
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Management

Motor

Parkinsonism:

- Carbidopa/levodopa, dopamine agonists
  - Sinemet®, Mirapex®, Requip®

  Deep brain stimulation (experimental)

Gait impairment/falls:

- Gait assistance devices and PT
- Power operated vehicle (POV)
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Management

Speech/Swallowing

Dysarthria/nonfluent aphasia/apraxia of speech:

- Speech therapy

? Carbidopa/levodopa, dopamine agonists
  - Sinemet®, Mirapex®, Requip®

Dysphagia:

- Swallowing study

- Thick-It, pureed food, PEG tube
Sleep Disorders

- Insomnia
- Daytime hypersomnia
- Obstructive sleep apnea
- Central sleep apnea
- Restless legs syndrome
- Periodic limb movements during sleep

* Discuss with primary MD, and in select cases, consider a formal sleep medicine evaluation and sleep study
Pathophysiology and Implications for Future Therapies
PSP, CBD, FTD, and PPA
Pathophysiology and Implications for Future Therapies

**Tauopathies**
- Pick’s disease
- Corticobasal degeneration
- Progressive supranuclear palsy
- Argyrophilic grain disease
- Frontotemporal dementia with Parkinsonism associated with mutations in microtubule associated protein tau on chromosome 17 (FTDP-17\textit{MAPT})

**TDP-43opathies**
- Frontotemporal lobar degeneration (FTLD) with motor neuron disease (MND)
- Frontotemporal lobar degeneration (FTLD) with ubiquitin/TDP-43-positive inclusions
- Frontotemporal dementia with Parkinsonism associated with mutations in progranulin on chromosome 17 (FTDP-17\textit{PGRN})
PSP, CBD, FTD, and PPA
Pathophysiology and Implications for Future Therapies

PSP

CBD

FTD

PPA

tau

TDP-43

amyloid
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Pathophysiology and Implications for Future Therapies

? Tauopathy therapies
- Microtubule stabilizers
- tau kinase inhibitors
- Hsp90 inhibitors
- tau aggregation inhibitors
  - davunetide
  - rember

Dickey & Petrucelli, Expert Opin Ther Targets 2006
PSP, CBD, FTD, and PPA

Pathophysiology and Implications for Future Therapies

Normal neuron

- progranulin
- degraded proteins

Abnormal neuron

- progranulin
- waste proteins
- clumped proteins
- Ubiquitin
- TDP-43+
Theoretical considerations for future experimental drug trials
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Pathophysiology and Implications for Future Therapies

Theoretical considerations for future experimental drug trials

Slowed progression with disease-altering therapy
Theoretical considerations for future experimental drug trials
Consider participating in research studies!!

Thank you!!
PSP, CBD, FTD, and PPA
Future Directions

• Increase awareness among the public and health care professions that PSP, CBD, FTD, and PPA exist, are recognizable disorders, and can be diagnosed and managed

• Develop networks of patients, families, friends, and health care professionals to improve managing the day-to-day aspects of the disorders

• Increase federal and private funding for research, education, and counseling

This is where you can help!
PSP, CBD, FTD, and PPA
Future Directions

- Refine the clinical, genetic, neuropsychological, radiologic, and pathologic characterization of the disorders that cause these disorders

- Improve our understanding of tau and TDP-43 protein physiology and pathophysiology so promising therapies can be developed and tested

- Identify and develop clinical, laboratory, neuropsychological, and radiologic measures for future therapeutic drug trials

Ultimately prevent, delay the onset, and slow the progression of the disorders that cause PSP, CBD, FTD, and PPA
Resources

(some of many excellent resources)
FTD and PPA
Resources - Websites

http://www.ftd-picks.org

http://www.brain.northwestern.edu/ppa/index.html
PSP and CBD
Resources - Websites

http://curepsp.org

http://www.ftd-picks.org
Questions?