Perspectives on Frontotemporal Dementia and Primary Progressive Aphasia

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Off-label and/or Investigational Use

- I will discuss use of some medications not FDA-approved for the indications to be reviewed
Perspectives on FTD and PPA
Outline

• Symptoms
• Brain-Behavior Correlations
• Genetics
• Pathophysiology and Future Perspectives
• Resources/Websites
Symptoms

Patient Examples
Brain-Behavior Correlations
FTD and PPA
Brain-Behavior Correlations

Templates

A B C

A

B

C
FTD and PPA
Brain-Behavior Correlations

- Thinking/Cognitive
- Behavior
- Language
FTD and PPA
Brain-Behavior Correlations

Memory - hippocampi
“Emotional valence”
- amygdala
FTD and PPA
Brain-Behavior Correlations

Problem-solving, reasoning, complex decision-making - dorsolateral frontal regions
Socially appropriate behavior, “theory of mind” - ventromedial frontal regions

FTD and PPA
Brain-Behavior Correlations
FTD and PPA
Brain-Behavior Correlations

Motivation, spontaneous actions - anterior cingulate region
Language - left frontal, temporal, parietal regions

FTD and PPA
Brain-Behavior Correlations

“A”
“Speech”
Naming

“B”
“Speech”, naming,
comprehension

“C”
Comprehension,
naming
FTD and PPA
Brain-Behavior Correlations

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

- Visual recognition - right > left temporal and occipital regions
FTD and PPA
Brain-Behavior Correlations

- Social disinhibition
- Loss of empathy and insight
- Ritualistic behavior
- Change in eating behavior
Memory loss

FTD and PPA
Brain-Behavior Correlations
Executive dysfunction
  Poor planning and judgement
  Inability to multitask

FTD and PPA
Brain-Behavior Correlations
Loss of motivation

Tendency to sit, not initiative conversations or actions
FTD and PPA
Brain-Behavior Correlations

- Poor verbal expression
- Poor naming of objects and people
- Poor comprehension and repetition

A B C

“A” “Speech output”
“A” “Naming”
“A” “Speech output”
“A” “Comprehension, repetition”

“Speech output”
FTD and PPA
Brain-Behavior Correlations

Aprosodia
Monotone voice
Unable to interpret inflections in voice another person’s voice
Visual agnosia
Unable to recognize objects and people
FTD and PPA
Brain-Behavior Correlations

Core features
- Behavioral disinhibition
  - Socially inappropriate behavior
  - Loss of manners or decorum
  - Impulsive, rash or careless actions
- Apathy or inertia
- Loss of sympathy or empathy
- Perseverative, stereotyped or compulsive/ritualistic behavior
- Hyperorality and dietary changes
  - Altered food preferences
  - Binge eating
  - Oral exploration or consumption of inedible objects

Rakovsky et al, International bvFTD Criteria Consortium
Core features

- Most prominent clinical feature is difficulty with language
- These deficits are the principal cause of impaired daily living activities
- Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease
FTD and PPA
Brain-Behavior Correlations

Core features
• Most prominent clinical feature is difficulty with language
• These deficits are the principal cause of impaired daily living activities
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Variants
• Nonfluent/agrammatic
• Semantic
• Logopenic

Mesulam MM. Ann Neurol 2001
Gorno-Tempini et al, Neurology 2011
FTD and PPA
Brain-Behavior Correlations

FTD

PPA
Genetics
FTD and PPA
Genetics

Approximately 10% of FTD cases are Inherited
(50% chance for each child and sibling for inheriting the gene and developing FTD)

40-75% of FTD cases are Sporadic
(Not Inherited)
Family members have general population risk

20-50% of FTD cases are Familial
(May be Inherited)
Family members are at increased, though undetermined, risk
FTD and PPA
Genetics

• ? Inherited form – if you have 1 or more 1st degree relatives with dementia and/or parkinsonism and/or ALS

• Genetic considerations:
  – Microtubule associated protein tau (clinical testing available)
  – Progranulin (clinical testing available)
  – Valosin-containing protein (VCP) (clinical testing not yet available)
  – CHMP2B (clinical testing not yet available)
  – TDP-43
  – FUS
  – Chromosome 9 gene not yet found
Pathophysiology and Implications for Future Therapies
FTLD - the pathologies

- Pick’s disease
- Corticobasal degeneration
- Progressive supranuclear palsy
- Multisystem tauopathy
- Frontotemporal dementia with Parkinsonism associated with mutations in microtubule associated protein tau on chromosome 17 (FTDP-17MAPT)
- 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-17PGRN)
- Dementia lacking distinctive histopathology (DLDH)

Alzheimer’s Disease
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-17MAPT)

**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-17PGRN)
FTD and PPA
Pathophysiology and Implications for Future Therapies

Tauopathies
- Pick’s disease
- CBD
- PSP
- AGD
- FTDP-17-MAPT

AGD
FTDP-17 MAPT

Pick

CBD

PSP
FTD and PPA
Pathophysiology and Implications for Future Therapies

TDP-43opathies
FTLD-U/TDP-43
FTLD-MND
FTDP-17-PGRN
ALS

ubiquitin

TDP-43

Josephs et al, JNEN 2007
FTD and PPA
Pathophysiology and Implications for Future Therapies

Tauopathies  TDP-43opathies
FTD and PPA
Pathophysiology and Implications for Future Therapies

? Tauopathy therapies
- Microtubule stabilizers
- Tau reducers (vaccine)
- Tau kinase inhibitors
- tau aggregation inhibitors
- Hsp90 inhibitors

Dickey & Petrucelli, Expert Opin Ther Targets 2006
FTD and PPA
Pathophysiology and Implications for Future Therapies

Normal neuron

Abnormal neuron

waste proteins

progranulin

degraded proteins

waste proteins

clumped proteins

Ubiquitin

TDP-43+
Abnormal neuron

Use drugs that increase production or secretion of progranulin

FTD and PPA
Pathophysiology and Implications for Future Therapies
Use drugs that increase production or secretion of progranulin
FTD and PPA
Pathophysiology and Implications for Future Therapies

Theoretical considerations for future experimental drug trials

[Diagram showing a line representing worsening across evaluations]
FTD and PPA
Pathophysiology and Implications for Future Therapies

Theoretical considerations for future experimental drug trials

![Graph showing slowed progression with disease-modifying therapy](image)

- Slowed progression with disease-modifying therapy
FTD and PPA
Pathophysiology and Implications for Future Therapies

Theoretical considerations for future experimental drug trials

![Graph showing improvement with disease-modifying therapy](image)
Without knowledge about the natural history of patients with FTD and PPA, we will not know where to start when promising medications are identified/developed.

This is one of many reasons involvement in research studies are so critical.
FTD and PPA
Pathophysiology and Implications for Future Therapies

If you participate in research - thank you!!

If you are interested in participating in research – please contact any of the staff at this conference.
FTD and PPA
Resources - Websites

http://www.theaftd.org

http://www.brain.northwestern.edu/index.html
FTD and PPA
Resources - Websites

FTD/PPA Genetics
http://www.theaftd.org/frontotemporal-dementias/genetics

The Frontal Lobes

Scientific American Frontiers
Make Up Your Mind
http://www.pbs.org/saf/1302/