Understanding the Basics of Frontotemporal Dementia (FTD), Lewy Body Dementia (LBD) and Vascular Dementia

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Off-label and/or Investigational Use

- Will discuss use of many medications which are not FDA-approved for the indications to be reviewed
Non-AD Dementias
Outline

• Overview
• Brain-behavior Associations
• Dementia with Lewy Bodies
• Frontotemporal Dementia and Primary Progressive Aphasia
• Vascular Dementia
Non-AD Dementias
Overview

Major Syndromes and Diseases

• Alzheimer’s disease (AD)

• Dementia with Lewy bodies (DLB)/Parkinson’s disease with dementia (PDD)

• Frontotemporal dementia (FTD)

• Vascular dementia (VaD)

• Other
  • Normal pressure hydrocephalus
  • Creutzfeldt-Jakob disease
Non-AD Dementias
Brain-Behavior Associations

Brain Templates
Non-AD Dementias
Brain-Behavior Associations

Abbreviations:
• Ach = acetylcholine – basal forebrain
• HCT = hypocretin-1 – hypothalamus
• HA = histamine – tuberomamillary nucleus
• DA = dopamine – substantia nigra
• 5-HT = serotonin – raphe nucleus
• GLU = glutamate – diffuse

Diagram:
- GLU
- HCT
- Ach
- HA
- DA
- 5-HT
- glycine, galanin
Non-AD Dementias
Brain-Behavior Associations

• Cognitive issues
• Neuropsychiatric issues
• Motor issues
• Sleep issues
• Autonomic issues
Non-AD Dementias
Brain-Behavior Associations

- **Thinking/Cognitive**
- **Behavior**
- **Language**
Non-AD Dementias
Brain-Behavior Associations

- Memory - hippocampi
Non-AD Dementias
Brain-Behavior Associations

“Emotional valence”
- amygdala
Non-AD Dementias
Brain-Behavior Associations

Problem-solving, reasoning, complex decision-making - dorsolateral frontal regions
Socially appropriate behavior, “theory of mind” - ventromedial frontal regions
Non-AD Dementias
Brain-Behavior Associations

Theory of Mind

A core aspect of human social cognition that is affected early and prominently in FTD.

Circuits in the frontal lobes are responsible for considering tasks requiring “theory of mind”
Non-AD Dementias
Brain-Behavior Associations

Motivation, spontaneous actions - anterior cingulate region
Non-AD Dementias
Brain-Behavior Associations

- **Language** - left frontal, temporal, parietal regions

- **A**
  - “Speech”
  - Naming

- **B**
  - “Speech”
  - “Speech”, naming, comprehension

- **C**
  - Comprehension, naming
Non-AD Dementias
Brain-Behavior Associations

- **Prosody** - right frontal, temporal, parietal regions

[Diagram showing brain regions labeled A, B, C]
Non-AD Dementias
Brain-Behavior Associations

Visuospatial - right parietal region

Diagram showing brain sections with highlighted regions.
Non-AD Dementias
Brain-Behavior Associations

- Motor functioning, walking, fine motor dexterity
Non-AD Dementias
Brain-Behavior Associations

- **Praxis** - left medial frontal, parietal regions

Diagram showing brain regions labeled A, B, and C, highlighted for praxis and motor planning.
Non-AD Dementias
Brain-Behavior Associations

Psychomotor speed, emotional control, continence
Non-AD Dementias
Syndromes/Disorders

But let’s first look at…

Alzheimer’s Disease
(AD)
Alzheimer’s Disease

Symptoms of Alzheimer’s Disease

Problems with:

• memory
• language
• executive functions
• visuospatial functions
• motivation
Mild Alzheimer’s disease

hippocampal degeneration
Alzheimer’s Disease

Normal → MCI → Mild AD → Moderate AD → Severe AD

Mild AD

Moderate AD

Severe AD

Normal

MCI

Alzheimer’s Disease
Alzheimer’s Disease

- **Normal**
- **MCI**
- **Mild AD**
- **Moderate AD**
- **Severe AD**

Progressive degeneration of neocortical neurons

Progressive degeneration of ACh-making neurons
Alzheimer’s Disease

Normal

AD
Alzheimer’s Disease

Symptoms reflect progressive loss of neurons in the basal forebrain (ACh) and neocortex.

Treatments are designed to:

• Increase amount of ACh at the synapse to improve cognition (donepezil - Aricept®, galantamine - Razadyne®, rivastigmine - Exelon®)

• Decrease activity of glutamate (which is presumably involved in excitotoxicity) – memantine (Namenda®)
Non-AD Dementias
Syndromes/Disorders

Dementia with Lewy Bodies (DLB)
or
Lewy Body Dementia (LBD)
Dementia with Lewy Bodies

Symptoms of Dementia with Lewy Bodies

Problems with cognition:
- memory
- language (verbal blocking)
- executive functions
- visuospatial functions
- motivation

Problems with other issues:
- perception and thought content (hallucinations, delusions)
- motor functioning (parkinsonism)
- sleep (very sleepy, RBD, leg jerks)
- autonomic functioning (BP, constipation, erectile dysfunction)
Cognition issues

- Mainly due to reduced Ach
- Reductions in other brain chemicals contributes to cognitive impairment
- Some degree of neuron cell loss too
Neuropsychiatric issues

- Hallucinations and delusions related to DA imbalance
- Depression related to low 5-HT
- Apathy – many causes

Dementia with Lewy Bodies
Motor issues

- The Parkinson’s disease-like features (parkinsonism) primarily relate to the reduction in DA
Sleep issues

- Daytime sleepiness, insomnia, and fragmented sleep relate in part to the loss in HCT and HA
- Acting out dreams (RBD) relates to changes in the dorsal pons
- Reduced DA and 5-HT also affects sleep
Dementia with Lewy Bodies

Autonomic issues

- Many autonomic changes related to changes in the spinal cord and peripheral nerves in and around the:
  - heart
  - stomach
  - intestines
  - bladder
  - sex organs
### Dementia with Lewy Bodies

**Neuropsychological Features**

<table>
<thead>
<tr>
<th>Cognitive Domains</th>
<th>Impairment</th>
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<tbody>
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Dementia with Lewy Bodies
MRI Features

Normal  
DLB  
AD
Dementia with Lewy Bodies
PET Features

Normal

DLB

AD

Occipital
Parietal

Temporal
Parietal
Frontal
Dementia with Lewy Bodies
Neuropathologic Features

Lewy body – comprised of alpha-synuclein protein
Dementia with Lewy Bodies

Symptoms reflect progressive loss of neurons in multiple nuclei which produce neurotransmitters, and to some degree loss of neurons in the neocortex. DLB is more of a neurochemical disruption disorder than AD, FTD, and VaD.

Treatments are designed to:

• increase or decrease acetylcholine, dopamine, serotonin, norepinephrine, and other brain chemicals

• management is complicated, and should be overseen by a clinician with experience in DLB treatment.
Non-AD Dementias
Syndromes/Disorders

Frontotemporal Degeneration (FTD)

Includes the syndromes of behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA)
Frontotemporal Degeneration

Symptoms of Frontotemporal Degeneration

Changes in cognition and/or language:
- memory
- language (aphasia)
- executive functions

Changes in behavior:
- loss of insight
- decreased empathy/sympathy
- social disinhibition
- impulse dyscontrol
- apathy
Frontotemporal Degeneration

- Behavioral Variant Frontotemporal Dementia (bvFTD)
- Primary Progressive Aphasia (PPA)

Brain diagrams showing regions affected in bvFTD and PPA.
Frontotemporal Degeneration

- Dorsolateral prefrontal, orbitofrontal, anterior cingulate, right >> left
Frontotemporal Dementia
Neuropsychological Features

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Frontotemporal Dementia

MRI Features

Amygdala atrophy

Frontal cortical atrophy
Frontotemporal Dementia
MRI Features - Longitudinal

Age 33

Age 35

Age 37
Frontotemporal Dementia
PET Features

Alzheimer’s Disease

Behavioral Variant Frontotemporal Dementia
Primary Progressive Aphasia
Topographic Distribution of Degeneration

- Dominant hemisphere, frontal and/or temporal cortex
# Primary Progressive Aphasia

## Neuropsychological Features

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Primary Progressive Aphasia
MRI Features

Nonfluent PPA
Semantic PPA
Logopenic PPA
Primary Progressive Aphasia
PET Features

Nonfluent PPA

Semantic PPA

Logopenic PPA
Frontotemporal Degeneration
Neuropathologic Features

tau

TDP-43
Frontotemporal Degeneration

FTD/PPA

Symptoms reflect progressive loss of neurons in right>left frontotemporal region (FTD) or left>right frontotemporal region.

Treatments are designed to:

• non-drug therapy – education and counseling, speech therapy

• drug therapy – management of target symptoms

• many therapies nearing readiness for clinical trials affecting tau, TDP-43, etc.
Non-AD Dementias
Syndromes/Disorders

Vascular Dementia (VaD)
Vascular Dementia

Features of Vascular Dementia

Problems with cognition:
- memory
- language
- executive functions
- visuospatial functions

Changes in behavior:
- apathy
- emotional lability

Changes in motor functioning:
- features of “stroke”
- gait impairment
Vascular Dementia

Core features:

• cognitive decline shortly after a stroke

• CT or MRI evidence of infarcts in structures involved in cognition

  or

• progressive cognitive decline, often with gait impairment and incontinence

• dramatic changes in white matter on MRI
Vascular Dementia

Key concepts:

• symptoms or findings correlate with the lesions (strokes) on MRI

• since strokes can occur in almost any region of the brain, the symptoms associated with vascular dementia varies widely from patient to patient
Vascular Dementia

Critical lesion(s):

- Left thalamus infarct
  - Memory impairment
  - Mild aphasia
- Right frontal infarct
  - Decreased empathy
  - Poor multitasking
- Left perisylvian infarct
  - Aphasia
  - Memory impairment
Vascular Dementia

Striking white matter changes

Poor multitasking
Slowed thinking
Forgetful
Parkinsonism
Incontinence
Vascular Dementia

Symptoms reflect which part(s) of the brain was affected by stroke(s).

Treatments are designed to:

• non-drug therapy – education and counseling, speech therapy
• drug therapy – management of target symptoms
• minimize risk of future stroke – weight loss, exercise, no smoking, treat high blood pressure and diabetes, treat sleep apnea
Non-AD Dementias

Thank you for your attention!