Behavioral and Neuropsychiatric Correlates of Alzheimer's Disease & Related Disorders

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Dementia

- Syndrome
- Multiple Cognitive Domains
- Change from Pre-Morbid Cognitive Status
- Impairment in Ability to Function

Cognitive Domains*

- Attention & Concentration
- Learning & Memory
- Executive Functioning
- Language & Verbal Functioning
- Visuospatial/Visuoconstructional Abilities
- Motor/Psychomotor Functioning

*As part of the clinical workup for dementias, neuropsych. evaluations usually inquire re: changes in ability to function in everyday life.

Dementia

- Dementias usually affect:
  - Cognition
  - Behavior and/or Personality
  - Psychiatric Functioning
- The order in which the above are affected and their relative prominence vary among the different dementias, among individuals with the same type of dementia, and at different stages of the disease process.

Behavioral & Neuropsychiatric Presentation (BNP)

- The BNP of a specific dementia is more identifiable in the early stages of the disorder. As conditions progress, they are more difficult to tell apart.
- Mixed Dementia: Neuropathology of more than one dementia syndrome. Example: High amyloid deposition accompanied by cerebrovascular changes and/or Lewy Bodies.
  - Complicates clinical picture

Dementia with Lewy Bodies (DLB)

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- DLB is the 2nd most common type of dementia in persons over 75 yrs.
- Characterized by progressive dementia, parkinsonism, & neuropsychiatric symptoms.
- Diagnosis is difficult due to frequent co-occurrence with AD & perceived similarity to movement disorders (e.g., PD).

Dementia with Lewy Bodies (DLB)

- Three primary symptoms:
  - Cognitive symptoms (e.g., early attention & visuospatial deficits with relatively preserved memory; fluctuations in alertness & attention)
  - Psychiatric symptoms: Hallucinations (usually visual), delusions, depression
  - Motor symptoms (e.g., parkinsonism with rigidity, tremor, shuffling gait). Frequent falls.

Dementia with Lewy Bodies (DLB): Epidemiology

- Progressive dementia with insidious onset.
- Progression: Slow (i.e., 5-7 yrs), but more rapid than AD
- In the U.S., the prevalence of “pure DLB” is about 5%. Estimate: Additional 20% of DLB occurs in the context of AD (i.e., AD + DLB)

Lewy Body Dementia *(Cont.)*

- Onset: Risk increases with older age
- Progression of signs & symptoms:
  - Psychiatric symptoms, particularly visual hallucinations, occur in early stages.
- Etiology: Accumulation of protein deposits known as Lewy bodies distributed throughout the cerebral cortex, basal ganglia, and other brain structures (e.g., Substantia Nigra, N. Basalis of Meynert)

Lewy Bodies (LBs)

- Lewy Bodies are pathological* aggregates of protein
- In addition to DLB, Lewy Bodies are usually found in brains of persons with other neurological conditions (e.g., PD)

*At autopsy, brains of older adults with no reported cognitive deficits have been found to have some LBs

Differential Diagnosis AD vs. DLB

- Psychiatric Sxs at onset are more common in DLB than in AD.
- More impairment than AD on executive functioning (particularly attention) and visuospatial ability, particularly in early stages.
- Memory problems usually appear later in the disease process.

Frontal Temporal Dementia (FTD)

Fronto-Temporal Dementia (FTD)

- Considered to be a subtype of a group of conditions known as Fronto-Temporal Lobar Degeneration (FTLD)
- Aka Behavioral Variant FTLD

Fronto-Temporal Dementia: Epidemiology

- Prevalence: ≈5% - 10% of all dementias
- In people under age 60, FTD is the most common type of dementia.
- Mean age of onset: ≈ 53 yrs, but can begin as early as 35 yrs of age
- Genetics: Strong genetic basis. Estimates: About 20% - 40% of cases have mutations in a gene associated with τ-protein (i.e., tau protein) in chromosome 17.

FTD: Clinical Presentation

- Profound early changes in the following domains:
  - Personality & Behavior (e.g., inappropriate jokes, disinhibition, lack of initiation, abulia)
  - Mood (e.g., depression, anxiety)
  - Cognitive Changes: Executive Functioning & Language are primarily affected
- Usually, in early stages, FTD does *not* present with memory problems.
- Because of the prominent behavioral, personality, & mood changes mentioned above, FTD is sometimes initially misdiagnosed as a psychiatric disorder.

FTD: Cognitive Presentation- Executive Functioning

- Executive Dysfunction: Cognitive hallmark of FTD. Typically presents in early stages, prompting family members to seek professional help.
- Most frequent executive dysfunction signs:
  - Behavioral Disinhibition
  - Impulsivity
  - Apathy
  - Loss of insight
- In addition to the above, attention is affected early, particularly selective and sustained attention.

FTD: Cognitive Presentation-Language Functioning

- Early problems with expressive language. This is characterized by reduced output, increased reliance on stereotypical remarks, verbal perseveration, & echolalia.
- Other aspects of language functioning are relatively preserved. These include receptive language (i.e., comprehension), naming, reading, & writing.
- In the moderate-severe stage, person is likely to evidence mutism.

FTD: Other Cognitive Domains

- Relatively preserved:
  - Visuospatial perception
  - Motor skills
- Memory problems usually develop in the moderate-to advanced stages of the condition.
  - Good consolidation of the information, difficulty with retrieval of the information (e.g., benefits from cues). Memory problems are not as pronounced in earlier stages, as they are in other dementias (e.g., AD).

FTD: Other Possible Problems

- Changes in ingestive behavior
- Hyperorality
- Hypersexuality
- Stereotyped & ritualistic behavior
- Repetitive behavior

FTD: Changes in the Brain

- Most pronounced change: Atrophy of the frontal lobes & the anterior temporal lobes.
- Pick's Bodies & τ-protein abnormalities predominate.
- Amyloid plaques or Lewy Bodies are not typically seen.

Vascular Dementia (VaD)

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- Impaired cognitive function that results from cerebrovascular disease (CVD) of ischemic or hemorrhagic origin, which affects brain areas that are important for memory and other cognitive processes and/or behavior.
- Early treatment of HTN, heart and vascular conditions can help prevent VaD. Prevention is key!

Epidemiology of VaD

- **Prevalence**: Estimates of prevalence vary considerably across studies. Estimates of prevalence of co-morbidity with AD also varies.
- **Gender**: More likely in men than women.
- **Age of Onset**: Usually 60-75 years of age.
- **Onset**: Diagnosis may follow an abrupt event (e.g., stroke).
- **Course & Progression**: Usually fluctuating, may be based on stepwise progression.

Epidemiology of VaD (Cont.)

- Clinical presentation of VaD, including its behavioral and neuropsychiatric manifestations, depends on a myriad of factors.
- Examples: The specific blood vessels involved; etiology of vascular event (e.g., large vs. small vessel disease, cortical vs. subcortical territories); gray matter vs. white matter; etc
- May present neurological and/or cognitive deficits that are more focal or “patchy” than the clinical presentation of the other dementias.

VaD vs. AD: Differential Diagnosis

- Risk factors: Cardiovascular history is usually prominent in VaD (not necessarily so in AD).
- Onset: May be abrupt in VaD (e.g., stroke-based) or stepwise (with additional cerebrovascular events). In AD, onset is insidious.
- Progression: May be stepwise in VaD. In AD, progression typically follows a more linear trajectory.
- Age at "onset"- VaD is more likely to occur at a younger age than AD.

VaD vs. AD: Differential Dx *(Cont.)*

- Gender distribution: More males than females in VaD; more females than males in AD.
- Clinical presentation: Neurological and cognitive signs and symptoms in VaD tend to be more focal and specific to affected area(s). AD presentation is more generalized.
- Cognitive presentation: Memory may or may not be affected in VaD, particularly in early stages. Memory impairment is characteristic of AD.

Alzheimer’s Disease (AD)

AD: *Some* of the Neurobiological Underpinnings

- ***Structural-Gross Neuroanatomy***
  - Cortical: General atrophy & loss of neurons in specific cortical regions
  - Subcortical: Structures important in memory (e.g., hippocampus)
- ***Structural- Neurohistological Changes*** (e.g., amyloid plaques & neurofibrillary tangles)
- ***Neurochemical***
  - Acetylcholine & glutamate
  - Other neurotransmitters

Neurohistological Changes of AD

- AD is characterized by the accumulation of amyloid plaques (extracellular) & neurofibrillary tangles (NFT, intracellular).
- Amyloid plaques consist mainly of β-amyloid peptides.
- Neurofibrillary tangles (NFT) consist of abnormal insoluble forms of the τ-protein.
- Both amyloid plaques and NFT exert direct & indirect neurotoxic effects in the brain and promote neuronal death & inflammation.

Tau (τ) Proteins *(Cont.)*

- A gene, in chromosome 17 is responsible for synthesis of τ-protein
- Under normal circumstances, tau protein is a highly soluble protein.
- Conditions with abnormal tau functioning are characterized by the self-assembly of tangles of paired helical filaments, which are insoluble and generate a cascade of intracellular events.

Common Behavioral & Neuropsychiatric Symptoms

- Agitation
- “Sundowning”
- Shadowing
- Wandering
- Depression
- Delusions and/or hallucinations
- Disinhibition
- Sleep disturbance
- Other

Things that May Complicate the Behavioral & Psychiatric Manifestations of Dementias

Possible Complicating Factors

a) **Physical Malaise or Discomfort** (e.g., pain, hunger/thirst, uncomfortable temperature, soiled underwear)
b) **Medication Adverse Side Effect** (e.g., anti-cholinergic, anti-adrenergic)
c) **Environmental** (e.g., too much/too little stimulation, noise)
d) **Consequences of Behaviors that May Place Person at Risk** (e.g., wandering, sundowning)
e) **Mixed Dementia**
f) **Emotional State**

Emotional State

- Depression & anxiety commonly coexist with conditions that affect the brain, and can contribute to cognitive symptoms.
- In dementia, depression & anxiety are difficult to assess, particularly in the moderate and more advanced stages.
- Assessment typically relies on report by informant, which is usually based on his/her behavioral observations (e.g., restlessness).