Differential Diagnosis of Dementias

George T. Grossberg, MD
Samuel W. Fordyce Distinguished Professor
Director, Geriatric Psychiatry
Department of Neurology & Psychiatry
St Louis University School of Medicine
Disclosures

• None for this presentation
Differential Diagnosis of Dementias
Presentation Overview

- Clinical evaluation for dementia
- Cognitive assessment tools
- Profiles of common dementias
- Imaging the different dementias
- Neuropsychiatric symptoms in dementias
Common Types of Neurodegenerative Dementia

- Alzheimer’s dementia (AD)
- Parkinson’s disease dementia (PDD)
- Dementia with Lewy bodies (DLB)
- Vascular dementia (VaD)
- Frontotemporal dementia (FTD)
- Mixed (multiple pathologies/etiologies) dementia

Lewy Body Dementia Spectrum

The Typical Dementia Scenario

- Patients may not seek medical care for symptoms
- Lack of insight common
- Patient denies problem, family/friends express concerns
- Caregivers may gradually compensate and cover up symptoms for the patient, "masking" the true magnitude of the deficits
- Delayed diagnosis until moderate stage

Core features of degenerative dementia

- Deficits in cognitive domains that may include memory
- Usually progressive deterioration
- Cognitive impairment interferes with social or occupational function
- Not attributable to another disorder

Clinical Evaluation for Dementia

**History**
- Obtain medical and psychiatric history, along with current symptoms
- Include collateral source such as family or other informant

**Physical, Neurologic, Mental Status Examinations**
- Identify neurologic deficits
- Conduct general screen for cognitive impairment

**Laboratory, Psychiatric, and Neuropsych Tests**
- **Identify reversible causes of cognitive impairment**
- Build on mental status examination, and provide clearer picture of pattern and degree of cognitive impairment

The “Dementia Workup”

- Detailed history from patient & reliable informant
- Head to toe physical & neurological examination
- Bloodwork (if not done recently) - CMP; CBC; TSH; B12/Folate; ?vit D; ?CRP; ?Homocysteine
- RPR, HIV testing (if indicated)
- Plain CT/MRI (one time); ?FDG-PET; ?amyloid-PET
- UA; CXRY (if indicated); EKG
- EEG, LP - not part of routine workup
Delirium is a Reversible Cause of Cognitive Impairment

Dehydration
Electrolyte/Endocrine disorder
Lack of oxygen
Injury/Impaction
Rule out psychiatric disorder
Infection
Urinary retention/Unfamiliar environment
Medications

## Delirium, Dementia, and Depression\(^1,2\)

<table>
<thead>
<tr>
<th></th>
<th>Delirium</th>
<th>Dementia</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Sudden</td>
<td>Insidious</td>
<td>Recent or recurrent</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Minutes to days</td>
<td>Months to years</td>
<td>Weeks to months</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>Reversible – resolves with treatment</td>
<td>Irreversible</td>
<td>Reversible, relapses common</td>
</tr>
<tr>
<td><strong>Consciousness</strong></td>
<td>Fluctuating</td>
<td>Generally alert</td>
<td>Generally alert, possibly withdrawn</td>
</tr>
<tr>
<td><strong>History of depression</strong></td>
<td>Usually negative</td>
<td>Usually negative</td>
<td>Usually positive</td>
</tr>
<tr>
<td><strong>Visuospatial</strong></td>
<td>Preserved</td>
<td>Often abnormal</td>
<td>Preserved</td>
</tr>
<tr>
<td><strong>Mood – Sadness/ Guilt/Worthlessness</strong></td>
<td>Absent</td>
<td>Usually absent</td>
<td>Usually Present</td>
</tr>
</tbody>
</table>

Examples of Cognitive Assessment Tools for the Office Setting

- Mini-Mental State Examination (MMSE)$^1$
- AD8 informant interview$^2$
- Mini-Cog assessment$^3$
- Montreal Cognitive Assessment (MoCA)$^4$
- St Louis University Mental Status (SLUMS) Examination$^5$

**Note.** These are assessment tools, and are not fully diagnostic of dementia.

---

Mini-Mental State Examination (MMSE)

- Brief, structured mental status examination for global cognitive function\(^1\)
- Typical deterioration of 3–4 points per year in a person with AD\(^2\)
- Sensitivity and specificity vary in different patient populations\(^3\)
- May be necessary to account for differences due to age, education, and ethnicity/race\(^3\)
- Does not specifically test episodic memory\(^1\)
- Copyright issues\(^3\)

<table>
<thead>
<tr>
<th>Score range, 0–30(^{1,3})</th>
<th>Unimpaired*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥28</td>
<td>Unimpaired*</td>
</tr>
<tr>
<td>20–27</td>
<td>Mild AD</td>
</tr>
<tr>
<td>10–19</td>
<td>Moderate AD</td>
</tr>
<tr>
<td>&lt;10</td>
<td>Severe AD</td>
</tr>
</tbody>
</table>

These cognitive scores may aid in identifying progression of dementia

* In a high-functioning patient, a MMSE score of ~28 could indicate impairment\(^3\)

1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking)

2. Less interest in hobbies/activities

3. Repeats the same things over and over (questions, stories, or statements)

4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)

5. Forgets correct month or year

6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)

7. Trouble remembering appointments

8. Daily problems with thinking and/or memory

The Informant Interview: The AD8

- Informant-based questionnaire
  - Can be administered at home or in waiting room
  - Yes/No format
- Detects change in individuals compared with previous level of function
  - No need for baseline assessment
  - Patients serve as their own control
  - Minimally affected by age, gender, race, and education
- Brief (<3 min), yes/no format
  - 2 or more “yes” answers highly correlated with dementia
  - Sensitivity, 85%
  - Specificity, 86%

Adapted from Galvin JE et al. The AD8, a brief informant interview to detect dementia. Neurology 2005;65:559-564. Copyright 2005. the AD8 is a copyrighted instrument of the Alzheimer’s Disease Research Center, Washington University, St. Louis, Missouri. All rights reserved.
Rapid Screen for Cognitive Impairment: Mini-Cog

- Rapid screen for cognitive impairment
  - 5 minutes to administer
    - 3-word registration
    - Simple clock-drawing test
    - 3-item recall
- Not influenced by education level or language
- Sensitivity, 99%
- Specificity, 93%

Montreal Cognitive Assessment (MoCA)

- Brief (10-min) cognitive screening test sensitive to domains involved in AD\(^1\)
- Demonstrated utility in PDD\(^2\)
- Includes measures in executive function\(^1\)
- Established utility in a multiple settings\(^1,2\)
- Test free for nonprofit use: http://www.mocatest.org/


Saint Louis University Mental Status Examination

• Designed to improve screening for mild neurocognitive disorder (MNCD)
• 11-item, clinician-scored scale

<table>
<thead>
<tr>
<th></th>
<th>High School Education</th>
<th>Less Than High School Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>27–30</td>
<td>25–30</td>
</tr>
<tr>
<td>MNCD</td>
<td>21–26</td>
<td>20–24</td>
</tr>
<tr>
<td>Dementia</td>
<td>1–20</td>
<td>1–19</td>
</tr>
</tbody>
</table>

• Study of SLUMS vs MMSE (N = 705)
  – *DSM-IV-TR®* criteria used to diagnose MNCD or dementia
  – Patients assessed by MMSE and SLUMS
  – Sensitivity and specificity
    • Dementia: similar for MMSE and SLUMS
    • MNCD: SLUMS appears superior to MMSE

### Rapid Brief Cognitive Screens: Pros and Cons

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE(^1,2)</td>
<td>Widely used, validated, reliable</td>
<td>Adjustments for age, education, and race may be necessary Copyright issues</td>
</tr>
<tr>
<td>AD8 informant interview(^3)</td>
<td>Reliable, sensitive, specific, rapidly administered</td>
<td>Knowledgeable informants may not be readily available</td>
</tr>
<tr>
<td>Mini-Cog assessment(^4)</td>
<td>Superior to MMSE in prediction of dementia status, rapidly administered, produces a visible performance indicator</td>
<td>Clock-drawing test scoring is vulnerable to varying interpretations</td>
</tr>
<tr>
<td>MoCA(^5,6)</td>
<td>Useful in patients with scores (&gt;25) on MMSE, strong executive function component</td>
<td>Conclusions regarding validity in PDD restricted to specialty clinic setting</td>
</tr>
<tr>
<td>SLUMS examination(^7)</td>
<td>Potentially superior to MMSE for early detection of cognitive impairment</td>
<td>Research needed to confirm applicability beyond initial study group</td>
</tr>
</tbody>
</table>

Note: insufficient information is available to determine whether any one screening tool is superior to another. Positive screening results should be followed by complete neurologic and medical examinations.

Profiles of Dementias
Alzheimer’s Dementia

- Multiple cognitive deficits, consisting of memory impairment and ≥1:
  - Aphasia
  - Apraxia
  - Agnosia
  - Executive function
- Each deficit causes significant impairment in social or occupational functioning

- Difficulty learning and remembering new information
- Repetitiveness, anomia
- Poor orientation to time

AD largely involves temporal-parietal deficits

Parkinson’s Disease Dementia

Core

- Develops in the context of established PD (>2 years)
- Cognitive and motor slowing with significant impairments in:
  - Executive function
  - Memory retrieval
- A decline from premorbid levels, with deficits sufficient to impair function

Clinical

- Slowing of cognitive processes/processing speed
- Fluctuating attention deficits
- Difficulties with abstraction and visuospatial skills

PDD affects the basal ganglia first, and disrupts ascending subcortical circuits

Dementia with Lewy Bodies

Core

- Fluctuating cognition with pronounced variations in attention and alertness\(^1\)
- Recurrent detailed visual hallucinations,
- Spontaneous features of parkinsonism\(^1\)
- Suggestive features\(^1\)
  - REM sleep behavior disorder
  - Severe neuroleptic sensitivity

Clinical

- Impairment in attention, visual perception and visual construction\(^1\)
- Memory is relatively spared early on, but deficit evident with progression\(^1\)
- Cognitive and motor symptoms often co-present

Vascular Dementia

- Decline in cognitive function from a prior baseline and a deficit in performance in ≥2\(^1\)
  - Executive/attention
  - Memory (may not always be impaired)\(^2\)
  - Language
  - Visuospatial function
- Evidence of cerebrovascular disease via neuroimaging\(^1,3,4\)
  - Focal neurological signs that may relate to vascular lesion location\(^1,3,4\)
  - Cognitive deficits may occur in a stepwise fashion\(^1,3,4\)

Frontotemporal Dementia

• FTD may be classified into various subtypes $^{1,2}$
  – Primary progressive aphasia (PPA)
    • Progressive nonfluent aphasia
    • Logopenic variant
    • Semantic dementia (SD)
  – Behavioral Variant (bvFTD)
• PPA primarily affects language early, whereas bvFTD may be classified as an early behavioral disorder $^1$
• FTD variants may overlap later in the disease course $^{1,2}$

Behavioral Variant of Frontal Temporal Dementia

- Progressive deterioration of behavior and/or cognition with ≥ 3 early:\(^1\)
  - Behavioral disinhibition
  - Apathy
  - Loss of sympathy/empathy
  - Perseverative, stereotyped or compulsive behavior
  - Hyperorality
  - Executive deficits with relative sparing of memory and visuospatial function
- Frontal and/or anterior temporal atrophy on MRI or CT\(^1\)
- Tactless and impulsive behavior\(^2,3\)

Imaging in the Diagnosis

- **Left** - AD shows prominent sulci in tempo-parietal areas, typically accompanied by ventricle enlargement
- **Middle** - VaD most often shows cerebrovascular lesions on T2-weighted MRI
- **Right** - FTD shows prominent sulci in frontotemporal areas with relative parietal and occipital sparing
Imaging: AD vs DLB

- AD can show marked hippocampal atrophy
- In DLB, the hippocampus may be relatively spared

# Neuropsychiatric Symptoms in Dementias

<table>
<thead>
<tr>
<th>NPI Item</th>
<th>AD</th>
<th>PDD</th>
<th>DLB</th>
<th>VaD</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>●</td>
<td>●</td>
<td>●●</td>
<td>●</td>
<td>-</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>-</td>
<td>●●●</td>
<td>●●</td>
<td>●</td>
<td>-</td>
</tr>
<tr>
<td>Agitation</td>
<td>●●</td>
<td>●●</td>
<td>●●●</td>
<td>●●</td>
<td>●●●</td>
</tr>
<tr>
<td>Depression</td>
<td>●●</td>
<td>●●●</td>
<td>●●●</td>
<td>●●</td>
<td>●</td>
</tr>
<tr>
<td>Anxiety</td>
<td>●●</td>
<td>●●●</td>
<td>●●●</td>
<td>●●</td>
<td>●</td>
</tr>
<tr>
<td>Apathy</td>
<td>●●●</td>
<td>●●●</td>
<td>●●●●</td>
<td>●●●</td>
<td>●●●●</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>●●●●</td>
</tr>
<tr>
<td>Irritability</td>
<td>●●</td>
<td>-</td>
<td>●●●</td>
<td>●●</td>
<td>●●●</td>
</tr>
<tr>
<td>Sleep</td>
<td>●</td>
<td>●</td>
<td>●●●</td>
<td>●●</td>
<td>●●●</td>
</tr>
</tbody>
</table>

- 0-14%
- 15-29%
- 30-44%
- 45-59%
- ≥ 60%
# Pathologic Profiles of Dementias

<table>
<thead>
<tr>
<th>Pathologic Signs</th>
<th>AD</th>
<th>PDD</th>
<th>DLB</th>
<th>VaD</th>
<th>bvFTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuritic plaques</td>
<td>●●●</td>
<td>●</td>
<td>●●</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NFTs</td>
<td>●●●</td>
<td>●</td>
<td>●●</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cortical Lewy bodies</td>
<td>-</td>
<td>-</td>
<td>●●</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subcortical Lewy bodies</td>
<td>-</td>
<td>●●●</td>
<td>●●●</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ischemic damage</td>
<td>●●</td>
<td>-</td>
<td>-</td>
<td>●●●</td>
<td>-</td>
</tr>
<tr>
<td>Tau or TDP-43 inclusions</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>●●●</td>
</tr>
</tbody>
</table>

### Biochemical Deficit

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>PDD</th>
<th>DLB</th>
<th>VD</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic</td>
<td>●●●</td>
<td>●●●●</td>
<td>●●●</td>
<td>-/-</td>
<td>-</td>
</tr>
<tr>
<td>Dopaminergic</td>
<td>●</td>
<td>●●●</td>
<td>●●●</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- Generally absent  Infrequent  Typical  Hallmark Feature  Severe Deficit

Current FDA-Approved Therapies

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>PDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Acetylcholinesterase Inhibitors¹</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Number of NMDA Antagonists¹</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

- AD symptoms correlate with disruption of cholinergic circuits²
- PDD is characterized by a larger cholinergic deficit than AD³
- There are no FDA-approved medications of any class to treat DLB, VaD, or FTD

The Importance of Making an Early Diagnosis

- Identify and treat reversible causes
- Help explain presence of troublesome behaviors
- Allow the patient to make critical life decisions
- Identify and treat psychiatric symptoms
- Maximize patient safety
- To provide treatment
- Allow caregiver early access to support and community resources

Caregiver Challenges in Different Types of Dementias

- AD – typically older onset, with frequent co-morbidities
- PDD – prominent motor symptoms leading to falls
- DLB – frequent and sometimes severe neuropsychiatric symptoms
- VaD – depression and continuing risk factors for stroke
- FTD - younger onset, predominant behavioral and language symptoms
Summary

• Diagnosis of dementia begins with recognizing cognitive impairment (CI) in the patient
  – Cognitive assessment tools can be valuable

• Reversible causes of CI should be ruled out via the dementia workup
  – Delirium must be ruled out, or if present, treated accordingly

• Key clinical features of each dementia can aid the clinician in arriving at the specific diagnosis

• Making the specific diagnosis early is critical for the patient and caregiver