Overview of Dementia Etiologies

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TODAY’S ROAD MAP

• MCI subtypes (in brief)
• Four Common Etiologies of Dementia
  • Alzheimer’s disease
  • Vascular-related
  • Frontotemporal
  • Lewy body
Cognitive Aging & Decline

- **Normal Aging**: Everyone experiences slight cognitive changes during aging.
- **Preclinical**
  - Silent phase: brain changes without measurable symptoms
  - Individual may notice changes, but not detectable on tests
  - “A stage where the patient knows, but the doctor doesn’t”
- **MCI**
  - Cognitive changes are of concern to individual and/or family
  - One or more cognitive domains impaired significantly
  - Preserved activities of daily living
- **Dementia**
  - Cognitive impairment severe enough to interfere with everyday abilities

Time (Years)
Mild Cognitive Impairment (MCI)

- DSM-5 Mild Neurocognitive Disorder
- Petersen criteria (1999)
  - Only considered memory impairment
- Revised Petersen criteria (2004)
  - Cognitive complaint by patient or family
  - Significant impairment (>1.5sd) in at least one cognitive domain
  - Intact daily functioning (ADLs/IADLs)
  - Single domain vs. Multiple domain
  - Amnestic vs. Non-amnestic

Petersen et al., 2004; Journal of Internal Medicine, Volume: 256, Issue: 3, Pages: 183-194, DOI: (10.1111/j.1365-2796.2004.01388.x)
Dementia

• DSM-5 Major Neurocognitive Disorder

• Evidence of significant cognitive decline from the previous level of performance in one or more cognitive domains based on:
  1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function, AND
  2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantifiable clinical assessment

• The cognitive deficits interfere with capacity for independence in everyday activities

• Not better explained by delirium, psychosis, mental health dx, other medical problem...

• Specifiers
  • Major NCD due to __________ (Alzheimer’s, Lewy Body, TBI, HIV, etc); Probable vs. Possible
  • With/Without behavioral disturbance
  • Severity: Mild (difficulties w/IADLs), Moderate (difficulties w/ADLs), Severe (fully dependent)
Dementia is an umbrella term to describe cognitive impairment that affects everyday life.

- **Alzheimer’s Disease**: 55-70%
- **Vascular**: 20-30%
- **Lewy Body**: 10-20%
- **Frontotemporal**: 10-15%

**Other Causes:**
- Mixed Dementia
- Parkinson’s disease
- Huntington’s disease
- TBI
- Substance Abuse
- HIV/”HAND”
Alzheimer’s Disease

• Most common cause of dementia
  • 5.8 million cases in U.S. currently
  • By 2050, U.S. 14 million cases (131 mil. globally)

• Females > Males

• Early onset (<65yo) versus Late onset (>65yo)

• Insidious onset, gradual decline

• Cardinal features: rapid forgetting, repetition, word finding problems, and executive deficits (problem-solving, reasoning)

• Pathology
  • “Tau Tangles” = Tau Protein aggregation
  • Beta Amyloid Plaque build-up
  • CSF studies and PET imaging can help identify Tau and Amyloid presence
Alzheimer’s Disease - Genetics

• Early-onset AD (<10% of AD cases)
  • “Familial” variant, autosomal-dominant
  • APP on Chrom. 21
  • Presenilin (PSEN) 1 on Chrom. 14
  • PSEN 2 on Chrom. 1
  • Single-gene mutations → abnormal protein development

• Late-onset AD (>65yo)
  • Apolipoprotein E (APOE) on Chrom. 19
  • Two alleles = APOE genotype
    • E2 – possibly protective*
    • E3 – neutral
    • E4 – increases risk
      • 1 copy = increases risk 2-3x
      • 2 copies = increases the risk by ~10x
      • NOT guaranteed that will get AD
Alzheimer’s Disease – Neuroimaging & Pathology

- MRI/Structural: Atrophy
  - Often non-specific/generalized
  - Medial temporal lobe
    - Hippocampus, entorhinal cortex

- PET: Decreased glucose metabolism
  - Posterior temporoparietal
  - Precuneus
  - Poster cingulate
Jack et al. (2013) Model of AD
**MEMORY**

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

<table>
<thead>
<tr>
<th></th>
<th>FACE</th>
<th>VELVET</th>
<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
<th>NO POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ST TRIAL</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>2ND TRIAL</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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**DELAYED RECALL**

Memory Index Score (MIS)

<table>
<thead>
<tr>
<th>MIS</th>
<th>Lead to words WITH NO CUE</th>
<th>FACE</th>
<th>VELVET</th>
<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
<th>Points for UNCUED recall only</th>
</tr>
</thead>
<tbody>
<tr>
<td>X3</td>
<td></td>
<td>⬗</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>X2</td>
<td>Category cue</td>
<td>✓</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>X1</td>
<td>Multiple choice cue</td>
<td>⬗</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
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</tbody>
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MIS = 3/15

**ORIENTATION**

<table>
<thead>
<tr>
<th></th>
<th>Date</th>
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<th>Year</th>
<th>Day</th>
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_0/5_
Vascular Dementia (VaD)

- Second most common cause of dementia
- **Acute** (e.g., stroke) or **Chronic**
  - Onset: Event-specific onset vs. insidious
  - Course: Step-wise vs. gradual
- Risk Factors: CAD, HTN, hyperlipidemia, DMII, OSA, COPD, afib, etc.
- Clinical Presentation: “Subcortical” pattern
  - Reduced processing speed, executive functioning, working memory
  - Retrieval deficits that can improve with recognition tasks
  - Apathy, depression, emotional blunting, bradyphrenia
Vascular Dementia - Neuroimaging

- Chronic small vessel ischemic changes
- Microhemorrhages
- Leukoaraiosis >25% on imaging*
  - White matter change near lateral ventricles
- “Binswanger’s Disease” = subcortical vascular dementia
MoCA for Amnestic vs. Non-amnestic Differentiation

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<td>FACE</td>
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<td>1ST TRIAL</td>
<td></td>
</tr>
<tr>
<td>2ND TRIAL</td>
<td></td>
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<table>
<thead>
<tr>
<th>ATTENTION</th>
<th>Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order. Subject has to repeat them in the backward order.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[ ] 2 1 8 5 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] F B A C M N A J K L B A F A K D E A A A J A M O F A A B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serial 7 subtraction starting at 100.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] 93</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LANGUAGE</th>
<th>Repeat: I only know that John is the one to help today. The cat always hid under the couch when dogs were in the room.</th>
</tr>
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<tr>
<td></td>
<td>__/2</td>
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<table>
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<tr>
<th>Fluency: Name maximum number of words in one minute that begin with the letter F.</th>
</tr>
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<td>[ ] _____ (N ≈ 11 words)</td>
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| AB abraction | Similarity between e.g. banana - orange - fruit | train - bicycle | watch - ruler | __/2 |

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<td></td>
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| ORIENTATION | Date | Month | Year | Day | Place | City | __/6 |

UW Medicine
### Vascular Dementia Example:

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Points for UNCUED recall only  
MIS = 10/15

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### Alzheimer's Disease Example:

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*Image by owMedicine*
Frontotemporal Dementia (FTD or FTLD)

- Typical onset in 50s (40-60), rapid decline
  - Men and women approximately equal; women more likely to have familial variant (C9orf72 mutation)
- Pathology: Tau, TDP-43, and many others
- Several Subtypes
  - Behavioral variant FTD (bvFTD)
    - “Frontal variant”
  - Primary Progressive Aphasia (PPA)
    - Semantic, Logopenic, Nonfluent/Agrammatic
- bvFTD Clinical Presentation
  - Personality/behavioral features often present first
    - Disinhibition, impulsivity, inappropriate social behaviors
    - “Not the person that I used to know”
  - Deficits in executive functioning, language, attention
  - Relatively spared memory and visuospatial skills
Dementia with Lewy Bodies (DLB)

- Cognitive, Psychiatric, and Motor features
- Typical onset 65-75yo, gradual decline
  - Cognitive/psych features first, then motor*
- Pathology: alpha-synuclein
- Males (3-4x) > Females; more rapid decline in men
- Clinical Features
  - Fluctuating cognition with pronounced variation in attention/alertness
  - Recurrent well-formed visual hallucinations
  - REM sleep behaviors and/or fragmented sleep
  - Parkinsonian features – bradykinesia, limb rigidity, postural instability
  - Apathy, depression
  - Deficits in executive functioning, processing speed, and visuospatial skills
Dementia with Lewy Bodies (DLB)

Please draw this figure:

A

Please draw this figure:

B

Draw a clock showing the time of 11:10:

C

D

E

F

Please draw this figure:

G

H

I

Boeve et al., 2008
Subjective cognitive complaints

Associated with non-neurologic conditions
  - Psychiatric, medical problems (e.g., sleep apnea), substance use, medication side effects

Clinical Features
  - Subjective complaints, detailed accounts and examples
    - “Great memory for memory problems”
  - Insidious, typically aligns with other conditions (mood, pain, etc)
    - Variability depending on symptoms
  - Improvements on cognitive testing with encouragement, cueing, or additional structure of tests
  - Many cognitive symptoms are reversible when underlying cause is treated
QUESTIONS?

Contact Information
Carolyn Parsey, PhD  cmparsey@uw.edu
UW Memory and Brain Wellness Center: www.depts.washington.edu/mbwc