Mild Cognitive Impairment

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Objectives

- Understand the risks for and causes of cognitive impairment
- Incorporate screening evaluation of patients at risk
- Plan treatment strategies to minimize the personal, social and financial impacts
Cognitive Continuum

Normal

Mild Cognitive Impairment

Dementia

Spectrum of cognitive changes

Asymptomatic
↓
Normal Cognitive Aging
↓
Subjective Cognitive Aging
↓
Mild Neurocognitive Disorder
↓
Major Neurocognitive Disorder
Cognitive functions that are vulnerable to the effects of aging

- Processing Speed
- Working Memory
- Long Term Memory
- Sensory Perception
- Inhibitory Control

*General control processes "executive functions"

Normal age-related cognitive decline

- Basic information processing (Gf)
- Basic cultural Knowledge (Gc)

Age 80: Learning & reasoning ability

Graph showing performance and intelligence measures over age.
Normal age-related cognitive decline
A finer-grained look

“Crystallized” intelligence [past learning]
- Breadth/depth of general knowledge (e.g., language)
- Accrued over lifetime based on fluid intelligence, education, interests

“Fluid” intelligence [on-the-spot learning & reasoning]
- Aptness in processing information (e.g., learning, reasoning, abstract thinking, problem solving)
- Includes executive function, working memory
- Reflects overall integrity of brain (speed, connectedness, etc.)

*This is the norm, but individuals vary a lot around the norm!


Mild neurocognitive disorder

- Cognitive decline abnormal for age and education but does not interfere with function and activities

- “At risk” state to develop a degenerative dementia

- When memory loss predominates, termed Amnestic MCI. This has ~15% per year of conversion to AD.
Mild neurocognitive disorder

- Significant, but less severe cognitive deficit
- Need to develop compensatory behaviors that limit the impact of cognitive decline
- May need more accommodation to maintain day-to-day function
- Interference with daily activities may not be noticeable but higher-level cognition is likely affected

What Is Dementia?

- Impairment in intellectual function affecting more than one cognitive domains
- Interferes with social or occupational function
- Decline from a previous level
- Not explained by delirium or major psychiatric disease
Major Neurocognitive Disorder (aka Dementia)

- A significant cognitive decline from a previous level of performance in one or more cognitive domains

- The cognitive deficits interfere with independence of everyday activities (i.e. iADLs)

- This is not delirium or another mental disorder

MCI: Definition and Subtypes

Cognitive Complaint
Not normal for age
Not demented
Cognitive Decline is objective
Essentially normal functional activities

MCI
Memory impaired?
- Amnestic MCI
- Non-Amnestic MCI

Memory impairment only?
- Amnestic MCI Single Domain
- Amnestic MCI Multiple Domain
- Non-Amnestic MCI Single Domain
- Non-Amnestic MCI Multiple Domain

Epidemiology: MCI

- Studies vary significantly due to:
  - Diagnostic criteria
  - Measuring instruments
  - Definitions
  - Use of population vs clinic-based samples

- Prevalence rate 2-4% to greater than 20%

Pathology: MCI

- Neuropathological studies suggest that MCI represents an early clinical expression of age-related neurodegenerative disease.

- Common autopsy findings have AD pathology, cerebrovascular disease, mixed type.
Evaluation: MCI

- The cornerstone of any evaluation of someone with memory loss is the clinical interview.

The HPI is critical!

- Ask a close informant
- Duration, rate, smoothness?
- Associated symptoms
  - Headache, trouble with vision, speech, strength, coordination, gait
- What domains are affected?
- How is function affected?
  - Finances, chores, hobbies, driving, occupation, social
Fill out the picture

- Medical problems and risk factors?
- Neurologic history (stroke, trauma, infection)?
- Educational background?
- Family history?
- Alcohol and drugs?
- Medications?

*Remember, your first goal is to exclude readily treatable causes...*

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**Example of Mild Cognitive Complaints**

- A 64 yo overworked accountant is behind in his work and overwhelmed. He worries that his memory is failing and that he can’t keep up with his responsibilities.

- He’s using lists and GPS more and more. He came close to missing an important appointment, but was reminded of it, at the last minute.

- Assessment: normal MRI, but low scores in **executive functioning and memory**.
Example of Mild Cognitive Complaints

- A 68 yo attorney is forgetting appointments and relying more on her GPS.
- Her car, in neutral, rolled out of the driveway and hit a car.
- She paid a large bill twice and never recorded it in her checkbook.
- Assessment: apparent mild decline in memory storage and executive function

OVERVIEW: Consider main syndrome & comorbid conditions

- Psychotic depression
- Schizophrenia with depression
- Schizophrenia with cognitive deficits
- PDD, LBD, AD, VaD with psychotic sx
- Depression with dementia ("pseudodementia")
- Vascular depression with mild cognitive impairment
- MCI with depression
- Dementia with depression
- PD with depression
- PDD, LBD, PD+ with cognitive deficits
- PDD, LBD, AD with movement sx
- Schizophrenia with movement disorders
SYMPTOM OVERLAP: OVERVIEW

- Depression
- Psychosis
- Dementia
- Movement disorders

Cognitive decline

- Gen. medical
- Gen. neurologic
- Hepatic, renal, or thyroid disease
  - Deficiency (B12)
  - Toxins, OSA
- Trauma, tumor,
  - MS, HIV, syphilis,
  - NPH, subdurals,
  - vasculitis, CJD
- Alcohol
  - Recreational
  - Prescriptions!
- Alzheimer
  - Vascular
  - Lewy body / PD
  - Frontotemporal

Alone, or With dementia

Many causes!
“Primary” dementias: the big ones

- AD = Alzheimer’s disease
- LBD = Lewy Body dementia
- PDD = Parkinson disease dementia
- FTD = Frontotemporal dementia
- Vascular

Alzheimer Disease (AD)

- Commonest neurodegenerative and dementing disease
- Prevalence doubles every 5 years after 65; ~50% of those older than 85
**AD Risk Factors**

- Age!!
- Mild cognitive impairment (MCI)
- ApoE-e4 positivity
- Family hx in first degree relative (especially if younger onset)
- Vascular risk (diabetes, heart disease, etc.)
- Low education and physical/social activity
- Female sex

**Mild-moderate AD**

**Severe AD**
AD Clinical Features

- Earliest cognitive symptoms are usually poor short term memory; loss of orientation
- Smooth, usually slow decline without dramatic short-term fluctuations
- Other domains involved with time
- So common that many variations are seen

AD: Behavioral & Psych

- Depression, anxiety
- Irritability, hostility, apathy
- Delusions, hallucinations
- Sleep-wake changes
- Sundowning
- Agitation
Dementia with Lewy Bodies (DLB)

- Relatively earlier occipital and basal ganglia degeneration
- Similar to Parkinson disease dementia
- $\alpha$-synuclein aggregates into Lewy bodies
- Concurrent AD pathology is common

DLB Clinical Features

- Dementia (early on, visuospatial and executive) PLUS
  - Core features
    - Parkinsonism
    - Recurrent early visual hallucinations
    - Fluctuations (clue: recurrent delirium evaluations)
  - Suggestive features include REM sleep disorder (dream enactment) & neuroleptic sensitivity
Frontotemporal Dementia (FTD)

- Average age of onset 58, rather than very old
- Often familial (30-50%)
- Overlap with progressive supranuclear palsy, ALS, and corticobasal degeneration
- Pathologic aggregates of tau or TDP-43

FTD clinical features

- Behavior and personality change (may be initially misdiagnosed as a psychiatric disorder)
- Executive dysfunction
- Progressive non-fluent aphasia
- May see parkinsonism or muscle weakness
Vascular Dementia

- Suspect when
  - Abrupt onset and/or stepwise decline
  - Fluctuating course
  - H/o stroke
  - Focal neurologic symptoms or signs

- Usually see bilateral infarcts

- Often associated with executive dysfunction, gait disorder, apathy, incontinence

“...evidence of chronic small vessel ischemic disease involving subcortical white matter”

- This is nondiagnostic and very common with age
- Changes may or may not be symptomatic
- ≠ “Vascular dementia”
- Don’t tell patients “Your scan showed strokes.”
Differential diagnosis in dementia: More common treatable causes

- Structural brain lesion (subdural bleed)
- Thyroid disease
- B12 deficiency
- Untreated sleep apnea
- Depression or anxiety
- Alcoholism
- Meds: Benzos, opioids, anticholinergics (diphenhydramine, bladder drugs, tricyclics), neuroleptics, dopaminergics, other sedatives
Examination

- General neurologic exam
  - Any focalities that suggest stroke?
  - Signs of parkinsonism or a gait disorder?

- Cognitive screen
  - Mini-mental (MMSE)
  - Mini-cog
  - Montreal Cognitive Assessment (MoCA)
  - SLUM

Holsinger et al JAMA. 2007;297(21):2391-2404
Diagnostic testing

- There is no “dementia test panel”
- For slowly progressive “typical” dementia in adults >65, most essential tests: B₁₂, TSH, brain image (CT is ok)
- Neuropsychology testing can help but not mandatory
- FDG- PET approved to differentiate AD from FTD
- Amyloid-PET has just been approved
- PET studies have little value in most cases and are expensive
- For younger patients, or rapid or atypical course, workup may be “tiered” to target range of diagnoses, emphasizing treatable causes

Preclinical Stages of Alzheimer’s Disease

- No symptoms, BUT early pathology
- Preventive Therapy??
- Mild Cognitive Impairment
- Alzheimer’s Disease
- Cognitive Function
- Normal aging
- 40s-60s
- Age
- Death
Identifying Asymptomatic At-Risk Adults

- **Neuroimaging**
  - Magnetic resonance imaging (MRI)
    - Structure – atrophy, white matter hyperintensities
    - Function – cerebral blood flow
  - Positron emission tomography (PET)
    - FDG-PET – glucose uptake patterns
    - Amyloid imaging – amyloid burden

- **Cerebrospinal fluid biomarkers**
  - β-amyloid, tau

- **Cognitive tests**

- **Genetic tests (APOE4 allele)**

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Alzheimer’s Disease Neuroimaging Initiative (ADNI)

- Currently in its third phase (ADNI, ADNI-GO, ADNI-2)
- Older controls (n=150), MCI (n=450), AD (n=150), subjective memory complaint (n=100)
- Developed standardized MRI, PET, CSF methods
- Identified earliest biomarker changes in AD pathology
- Elucidated patterns & rates of change of imaging & CSF biomarkers in controls, MCI, & AD pts
- Identified at-risk participants for clinical trials

Hippocampal Atrophy in AD


Neuroimaging for Alzheimer’s Disease

Blinnlow K et al. Lancet 2006; 368: 387–403
Treatment: MCI

Summary

Table 3—Diagnostic Features and Treatment of Dementia Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Onset</th>
<th>Cognitive Domains, Symptoms</th>
<th>Motor Symptoms</th>
<th>Progression</th>
<th>Imaging</th>
<th>Pharmacologic Treatment of Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild cognitive impairment</td>
<td>Gradual</td>
<td>Primarily memory</td>
<td>Rare</td>
<td>Unknown, 12% per year proceed to Alzheimer disease</td>
<td>Possible global atrophy, small hippocampal volumes</td>
<td>Cholinesterase inhibitors (Chis) possibly protective for 18 months (SOE=1A) in subset of high-risk patients</td>
</tr>
<tr>
<td>Alzheimer disease</td>
<td>Gradual</td>
<td>Memory, language, visuospatial</td>
<td>Rare early, apraxia later</td>
<td>Gradual (over 3–10 years)</td>
<td>Possible global atrophy, small hippocampal volumes</td>
<td>Cholinesterase inhibitors (Chis) for mild to severe (SOE=1A); memantine for moderate to severe stages</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>May be sudden or stepwise</td>
<td>Depends on location of ischemia</td>
<td>Correlates with ischemia</td>
<td>Gradual or stepwise with further ischemia</td>
<td>Cortical or subcortical changes on MRI</td>
<td>Consider Chis for memory deficit only (SOE=1C), risk factor modifiers</td>
</tr>
<tr>
<td>Lewy body dementia</td>
<td>Gradual</td>
<td>Memory, visuospatial, hallucinations, fluctuating symptoms</td>
<td>Parkinsonism</td>
<td>Gradual but faster than Alzheimer disease</td>
<td>Possible global atrophy</td>
<td>Cholinesterase inhibitors (Chis=B); carbidopa/levodopa for movement</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>Gradual; age &lt; 60 years</td>
<td>Executive, disinhibition, apathy, language, memory</td>
<td>None</td>
<td>Gradual but faster than Alzheimer disease</td>
<td>Atrophy in frontal and temporal lobes</td>
<td>Not recommended per current evidence</td>
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</tbody>
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