Overview of Dementia

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Case Study - Mrs. Elder

- 81 year old with 3 year history of cognitive impairment and short term memory loss
- Patient does not feel that her memory loss is as bad as her husband says
- Impaired recent memory; repeating questions and misplacing items more often
- Difficulties with Instrumental Activities of Daily Living (IADL): no cooking the last 6 months; not taking inventory leading to impaired decision making while shopping

Dementia Definition

- Syndrome of acquired persistent intellectual impairment
- Persistent deficits in memory and at least one of the following sufficient to affect daily life:
  - Memory
  - Language
  - Visuospatial
  - Personality or emotional state
  - Cognition

Prevalence of Dementia Syndromes

AD = Alzheimer’s disease; DLB = Dementia with Lewy bodies; FCD = Focal cortical degeneration
Prevalence of Dementia Increases with Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percent Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 - 74</td>
<td>50%</td>
</tr>
<tr>
<td>75 - 84</td>
<td>3%</td>
</tr>
<tr>
<td>85 +</td>
<td>47.20%</td>
</tr>
</tbody>
</table>

Evans, et al. JAMA 1989;262:2551-2556

Steps in Diagnosis

- History
- Physical Exam
- Mental Status Exam
- Laboratory Evaluations
- Neuroimaging

Importance of Early Diagnosis of Dementia

- Plaques probably start 20 years before clinical symptoms of AD
- 16 million projected to have AD by 2050
- Current AD meds work better if started earlier
- Disease modifying agents are coming
- Preventing or delaying AD could save billions of dollars and lead to improved quality of life for patients and families

History

- Onset
- Clinical course
- Past medical history
- Psychiatric illness
- Medications
- Social and family history
History

- **Onset**
  - Abrupt
  - Subacute
  - Insidious

- **Course**
  - Stepwise
  - Progressive
  - Static

- **Disease State**
  - Vascular dementia
  - Neoplastic
  - Depression
  - Subdural
  - Trauma
  - Rapidly evolving dementias
  - Alzheimer’s disease
  - Frontotemporal dementia
  - Dementia with Lewy bodies
  - Normal pressure hydrocephalus
  - Huntington’s disease

Physical Exam

- **Normal:**
  - AD
  - FTD
  - Depression

- **Apraxia Only:**
  - AD
  - FTD
  - NPH (gait apraxia)

- **Movement tone, and gait abnormalities:**
  - Vascular dementia
  - Dementia with Lewy bodies
  - Parkinson’s disease
  - Huntington’s disease
  - Rapidly evolving dementias

Physical Examination

- Systemic illness
- Endocrine dysfunction
- Neurologic focal findings
- Movement disorders
- Gait apraxia and incontinence (classic for normal pressure hydrocephalus)

Mental Status Exam

- Attention
- Language
- Memory
- Visuospatial skills
- Abstraction and calculations
- Judgment and executive function
- Personality and emotional state
<table>
<thead>
<tr>
<th>Cortical vs Subcortical</th>
<th>Cortical vs Subcortical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Speech</strong></td>
<td><strong>Executive</strong></td>
</tr>
<tr>
<td>• Cortical: Normal, Stereotypy</td>
<td>• Cortical: Impaired sequencing, apraxia, poor judgment &amp; insight, ↓ verbal fluency</td>
</tr>
<tr>
<td>• Subcortical: Hypophonic, dysarthric</td>
<td>• Subcortical: Similar only if frontal-subcortical nuclei circuits involved</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td><strong>Visuospatial</strong></td>
</tr>
<tr>
<td>• Cortical: Anomia, aphasia</td>
<td>• Cortical: Abnormal orientation and constructions</td>
</tr>
<tr>
<td>• Subcortical: Normal</td>
<td>• Subcortical: Abnormal constructions</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
</tr>
<tr>
<td>• Cortical: Amnesia</td>
<td></td>
</tr>
<tr>
<td>• Subcortical: Retrieval deficit (forgetful)</td>
<td></td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td></td>
</tr>
<tr>
<td>• Cortical: Acalculia, poor judgment, impaired abstraction</td>
<td></td>
</tr>
<tr>
<td>• Subcortical: Slow processing speed, dilapidated</td>
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</tbody>
</table>
Mental Status

Cortical:
- AD
- FTD: spares posterior cortical deficits

Subcortical:
- Depression
- Vascular dementia
- NPH
- Parkinson’s disease dementia
- Huntington’s disease

Mixed Cortical and Subcortical:
- Vascular dementia
- Dementia with Lewy bodies
- Rapidly evolving dementias

AD = Alzheimer’s disease; FTD = Frontotemporal dementia; NPH = Normal pressure hydrocephalus

Examples of Cognitive Screening Tests

- MMSE
- Clock Drawing Test
- Mini-Cog
- AD8
- 7-minute Screen
- Montreal Cognitive Assessment (MOCA)
- Self-Administered Gerocognitive Examination (SAGE):

Mini-Cog

Figure 1. The Mini-Cog scoring algorithm. The Mini-Cog uses a three-item recall test for memory and a nine-item clock-drawing test. The latter serves as an “informative distractor,” helping to clarify scores when the memory recall score is intermediate.
Self-Administered Gerocognitive Exam (SAGE)

- Available at: www.sagetest.osu.edu
- Score: 0 (worst) - 22 (best)
- Tests orientation, memory, language, fluency, naming, visuospatial, abstraction, calculations, executive functioning, and problem solving
- Self-administered, easy to use
- Limited memory evaluation; excellent executive measures
- Takes 10 to 15 minutes; needs no examiner

Case Study - Mrs. Elder

- SAGE = 13 (-1 date off by two, -1 named volcano an explosion, -1 cube incorrectly copied, -1 named only 10 animals, -1 mild impairment in Trails B, -2 Problem solving task, -2 memory question)
- MMSE = 25 (-1 date, -1 serial 7s, -2 memory, -1 pentagons)
- Mini-Cog = dementia (impaired clock, -2 memory)

Laboratory Evaluation

Recommended for all dementias
- CBC
- Electrolytes, calcium, glucose, BUN, creatinine, LFT
- B12, folate
- TSH, T4
- FTA
Optional Evaluations

Consider for rapidly evolving dementias

- Sed rate, inflammatory markers
- HIV, Lyme
- CXR, EKG
- Urinalysis
- Assays for heavy metals, toxins
- LP
- EEG

Neuroimaging

- CT or MRI - neoplasms, abscesses, infarctions, white matter diseases, hydrocephalus, and subdural hematomas

- SPECT or PET - degenerative dementias

Gray Matter Reductions in AD Using Voxel Based Morphometry

Typical AD PET Scan
PET with Pittsburgh Compound B (PIB)

- PIB is a hydroxylated benzothiazole PET tracer
- Attaches to the amyloid beta peptide
- MCI patients have more amyloid than normals and less that AD patients


Normal Pressure Hydrocephalus

FTD SPECT Scan

Subcortical Vascular Dementia

Sachdev et al., Medical Journal of Australia 1999; 170: 81-85

FTD SPECT Scan

Sachdev et al., Medical Journal of Australia 1999; 170: 81-85
Summary

**Dementia Diagnosis**
- Dementia syndromes fit specific patterns
- History: Onset (acute, subacute, insidious), Course (stepwise, progressive, static)
- Exam: Normal, apraxia only, movement / tone / gait abnormalities
- Mental status: Cortical, subcortical, mixed
- Laboratory and imaging: Helps to differentiate these conditions

**Cognitive Rx in AD**

**Efficacy of Cholinesterase Inhibitors**
- Donepezil, Rivastigmine, Galantamine
- All of them work
- Up to 80% of patients show no decline after 6 months of Rx and 50% no decline after 1 year
- Need to give for at least 6 to 12 months to determine utility
- Always titrate to highest dose
### Cognitive Rx in AD

**Side Effects of Cholinesterase Inhibitors**
- Nausea/vomiting
- Diarrhea
- Anorexia
- Dyspepsia
- Leg cramps
- Agitation

### Disease-Specific Treatments

- Stroke prevention - Aspirin, clopidogrel, aspirin plus dipyridamole, coumadin, eliminate sources of emboli, control risk factors
- Vascular dementia treatment - Cholinesterase inhibitors
- Parkinson’s dementia - Dopaminergic agents; rivastigmine

### Cognitive Rx in AD

**NMDA Antagonists: Memantine**
- N-methyl-D-aspartate (NMDA) antagonists potentially prevent neuronal injury by reducing excitatory amino acid toxicity by glutamate
- Side effects include headache, dizziness, fatigue, confusion
- Titrate to 10 mg bid

### Disease-Specific Treatments

- Subdurals, neoplasms - Surgical treatment may help
- Normal pressure hydrocephalus - CSF shunting
- Toxins - Remove offending agents, chelation
Disease-Specific Treatments

- Metabolic dementias - Treat underlying condition
- Infectious dementias - Antibiotics, anti-virals
- Depression - Antidepressants, electroconvulsive therapy

Overview

- Approach to the patient with memory loss
- Diagnosis
- Differential diagnosis
- Standard of care for evaluation and treatment

Dementia

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Assistant Professor of Neurology
The Ohio State University

Historical Data…

On a Peculiar Disease of the Cerebral Cortex; A. Alzheimer (1907)

A woman, 51 years old, showed jealousy towards her husband... Soon, rapidly increasing loss of memory could be noticed... At times she would think that someone wanted to kill her.... She was totally disoriented to time and place... Periodically, she was totally delirious,...and seemed to have auditory hallucinations.... When reading, she went from one line into another, reading the letters or reading with senseless emphasis...

When talking she frequently used perplexing phrases and some paraphasic expressions (milk-pourer instead of cup)...

She seemed no longer to understand the use of some objects...

The generalized dementia progressed... After 4 1/2 years of the disease, death occurred.
**Definition**

- Development of multiple cognitive deficits manifested by
  - Memory impairment
  - One of the following cognitive disturbances
    - Aphasia
    - Apraxia
    - Agnosia
    - Disturbance in executive function
- The cognitive deficits cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning
- The deficits do not occur exclusively during the course of a delirium

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**Clinical Features**

- Orientation
- Abstract thinking
- Short term memory
- Long term memory
- Language
- Speech
- Praxis
- Perceptual problems
- Apathy
- Bradykinesia
- Behavior
- Gait

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**Diagnosis**

- DSM-IVR Diagnostic Criteria for Dementia of the Alzheimer’s Type
- NINCDS-ADRDA criteria for clinical diagnosis of Alzheimer’s Disease

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**A method for estimating disease duration on illness in Alzheimer’s disease**

- Set of questions to generate an estimate regarding the date of first symptoms to nearest half year
- Physicians revised the estimate in conjunction with medical record review and patient informant interview and by testing the estimate by recall of life events.

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A method for estimating disease duration on illness in Alzheimer’s disease

- 36 patients rated independently by two physicians.
- Physician rating was compared to each other and to an unstructured caregiver estimate of duration using Lin concordance coefficients.
- There was excellent agreement between independent physician raters (p=0.95, p<0.001)
- Caregiver’s estimate of duration were usually shorter because of failure to relate the first symptoms to the onset of the disease.

What are we testing?

- Does the patient:
  - Forgets where has left things,
  - Known phone numbers,
  - Becomes confused as to time, place, correct age and personal information,
  - Have trouble making decisions or solving problems
  - Repeat himself.

What are we testing?

- Does the patient:
  - Trouble balancing the checkbook,
  - Difficulty operating a TV set,
  - No longer driving because of memory difficulties,
  - Difficulty dialing the phone,
  - Traveling alone,
  - Get lost in own home.
What are we testing?

- Does the patient
  - Mood changes (anger, disinterest, sadness),
  - Appear anxious, nervous,
  - Antisocial behavior (agression, irritability), suspicious manner,
  - Hallucinations
  - Confuse one person with another,
  - Misidentify common objects,
  - Delusions,
  - Changes in activity level

The 3 Ds in the differential diagnosis

- Dementia
- Delirium
  - Acute confusional state
  - Attention, concentration deficits,
  - Fluctuations,
  - Psychomotor and or autonomic overactivity,
  - Fragmented speech, hallucinations
- Depression

VITAMINS
Mnemonic for Differential Categories of RPDs

- Vascular
- Infectious
- Toxic-Metabolic
- Autoimmune
- Metastases
- Iatrogenic
- Neoplastic/Neurodegenerative
- Systemic
Differential Diagnosis

- Neurodegenerative dementias
  - Alzheimer’s disease
  - Lewy Body Dementia
  - Frontotemporal dementia
  - Huntington’s disease
  - Progressive supranuclear palsy
  - Corticobasal ganglionic degeneration
  - Multiple system atrophy
  - Wilson’s disease
  - Hemochromatosis/hemosidirosis
  - Neuronal ceroid lipofuscinosis

Differential Diagnosis

- Vascular diseases
  - Vascular dementia
  - Cerebral amyloid angiopathy
  - Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
  - Vasculitis

80 yo WM with three years history of slowly progressive cognitive deficits.
MMSE 21/30
B12, TSH nl
80 yo WM with AF episodic confusion and progressive cognitive deficits

Differential Diagnosis

- Prion Diseases
  - Creutzfeldt-Jacob disease
  - Gerstmann-Straussler-Scheinker syndrome
  - Kuru
  - Fatal familial insomnia

- Structural abnormalities
  - Chronic subdural hematomas
  - Normal pressure hydrocephalus
  - Primary brain tumors (meningiomas/gliomas)
  - Metastatic disease
  - Paraneoplastic syndromes

64 yo wf with 2 years h/o gait apraxia, urinary incontinence and dementia
<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Demyelinating disorders</td>
<td>• Infections</td>
</tr>
<tr>
<td>• Multiple sclerosis</td>
<td>• HIV</td>
</tr>
<tr>
<td>• Leukodystrophies</td>
<td>• Neurosyphilis</td>
</tr>
<tr>
<td>• Traumatic brain injury</td>
<td>• Progressive multifocal leucoencephalopathy</td>
</tr>
<tr>
<td>• Metabolic disorders</td>
<td>• Subacute sclerosing pancephalitis</td>
</tr>
<tr>
<td>• Hepatic encephalopathy</td>
<td>• Whipple disease</td>
</tr>
<tr>
<td>• Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>• Storage disorder</td>
<td></td>
</tr>
<tr>
<td>• Nutritional disorders</td>
<td>• 39 yo WM with HIV/AIDs, incidental diagnosis three years ago, now with frontal dysexecutive dysfunction and hypersexuality.</td>
</tr>
<tr>
<td>• Vitamin B12 deficiency</td>
<td>• MMSE 22/30</td>
</tr>
<tr>
<td>• Thiamine deficiency</td>
<td></td>
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<tr>
<td>• Wernicke’s encephalopathy</td>
<td></td>
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<tr>
<td>• Wernicke-korsafoff’s syndrome</td>
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<tr>
<td>• Mitochondrial disorders</td>
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<tr>
<td>• Toxic disorders</td>
<td></td>
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<tr>
<td>• Alcoholism</td>
<td></td>
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<tr>
<td>• Drugs</td>
<td></td>
</tr>
<tr>
<td>• Heavy metals</td>
<td></td>
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</tbody>
</table>
Dementia syndromes associated with alcohol

- Amnestic syndrome (Korsakoff’s)
  - Amnestic disorder predominates-confabulations
  - Generalized dementia associated with alcoholism
  - Visuospatial impairment
- Alcohol related delirium-Wernicke’s encephalopathy
  - Confusion, eyes abnormalities and ataxia

Epidemiology of Alzheimer’s

- 4,000,000 Americans have AD
- 14,000,000 will have it by 2050
- $50-$90 billion/year health care cost
- People >60 y o ↑ 180% until 2030 (from 488 to 1363 millions)
- Older population ↑ 76.3% (from 203 to 358 millions)

Circuit of Papez

Epidemiology of Alzheimer’s

- Prevalence:
  - 1% in 60-64
  - 2% in 65-69
  - 4% in 70-74
  - 8% in 75-79
  - 16% in 80-85
  - and approximately 35 to 40% over the age of 85

- Incidence:
  - 2.5% for subjects aged 75 to 79
  - 5% for those 80 to 85
  - and almost 10% for those aged 85 and older
NINCDS-ADRDA Criteria

- Definite AD: clinical criteria for probable and histopathologic evidence from autopsy or biopsy
- Probable AD
- Possible AD
- Mild cognitive impairment-memory impairment only

Practice Recommendations

- Structural neuroimaging (Guideline).
- Depression (Guideline).
- B12 deficiency (Guideline).
- Hypothyroidism (Guideline).

Knopman et al. Neurology Volume 56 • Number 9 • May 8, 2001

Staging Scales/Time in Alzheimer’s disease

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Incipient or ? AD</th>
<th>Mild</th>
<th>Mod</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR Stage</td>
<td>0.5</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4, 6</td>
</tr>
<tr>
<td>GDS</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>MMSE</td>
<td>29</td>
<td>26</td>
<td>15</td>
<td>10</td>
<td>5</td>
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</tbody>
</table>

Cost Saving as a result of preventing cognitive decline

- A pharmacoeconomic analysis of the cost savings resulting from AD treatments predicted that the prevention of a small decline in a patient’s initial MMSE score would result in considerable savings below initial score of 12

Current Prevention

- Screening of patients elderly 65 years old by health care providers.
- Standardized questionnaires assessing cognition, function, mood, behaviors
- Early diagnosis and treatment
  - Clinical and financial benefit
  - Alleviate patient and caregiver burden
  - Reduce hospitalization time
  - Delay admission to NH