Objectives

- Distinguish memory loss from dementia
- Describe symptoms of dementia
- Discuss causes of dementia, particularly Alzheimer’s disease (AD)
- Describe therapeutic approach to Alzheimer’s disease
- Discuss possible future therapies
- Discuss issues pertaining the caregiver, and issues of medical advance directives

Memory Change with Age.

A spectrum.

- Memory worry
- Age associated memory change
- Mild cognitive impairment
- Dementia

Age-Associated Memory Change

- Usually self aware of memory change
- Often with time will think of forgotten item
- Types of memory loss
  - Recent events
  - Names of persons more than faces
  - "Tip of tongue"
  - Words in middle of sentence
- Retention of other cognitive skills

Age-Associated Memory Change

- 40% of people aged 65 or older have memory loss (16 million people)
- Not associated with functional impairment (normal functioning)
- Only 1% will develop Alzheimer’s disease
**Mild Cognitive Impairment**
- Memory complaint, preferably corroborated by an informant
- Objective memory impairment
- Intact activities of daily living

**Dementia**
- Insidious onset, chronic, progressive
- Multiple cognitive defects
- Significant impairment in social or occupational function
- Significant decline from a previous level of functioning
- Ultimate irreversibility

**Cognitive Functions**
- General intelligence
- Memory and learning
- Language
- Problem solving
- Orientation
- Perception
- Attention and concentration
- Judgement
- Social abilities
- Insight
- Personality

**Signs of Dementia**
- Learning and retaining new information
  - Such as trouble remembering events
- Handling complex tasks
  - Such as balancing a checkbook
- Reasoning
  - Like inability to cope with unexpected events
- Spatial ability and orientation
  - Like getting lost in familiar places
- Language, like word finding, dysnomia
- Behavior
**Mini Mental Status Examination (MMSE)**

1. **Orientation**
   - What is the date
   - What is the name of this place

2. **Registration**
   - Repeat three simple words

3. **Short term memory**
   - Repeat same three words in 3-5 minutes

4. **Attention and calculation**
   - Count backwards from 100 by 7s

5. **Name three objects**
   - Repeat "No, ifs ands, or buts"
   - Follow a three step command

6. **Write a sentence**

7. **Copy a design of intersecting pentagons**

**MMSE**

5. Name three objects
   - Repeat "No, ifs ands, or buts"
   - Follow a three step command

6. Read and follow a command

7. Write a sentence

8. Copy a design of intersecting pentagons

**Clock Drawings**

Attempts to copy intersecting pentagons by a patient with Alzheimer's disease at one-year intervals:

- Year 1
- Year 2
- Year 3
- Year 4

**Clinical Progression of AD and MCI**

- Normal function
- MCI
- Mild AD
  - MMSE 24-30
  - Mild subjective/objective memory
  - Normal function
- Moderate AD
  - MMSE 10-17
  - Progression of subjective deficits
  - Short-term memory loss
  - Word-finding difficulties
- Severe AD
  - MMSE 0-9
  - Alzheimer’s
  - Alteration sleep patterns
  - Total dependence dressing, feeding, bathing

- Time (y) Time (y)
- Normal
- Mild AD
- Moderate AD
- Severe AD

Clock Drawing Test — 2:45

- Normal
- Mild AD
- Moderate AD
- Severe AD
**Dementia: Clinical Presentation**

**Early phase**
- Insidious and vague
  - Somatic complaints
  - Depression, anxiety, paranoid, moody
  - Effort needed to complete normal, easy tasks
  - Excessive use of notes, lists, schedules
- Early signs of memory disturbance
  - Patient unaware
  - Diminished drive, interest, creativity, satisfaction

**Middle phase**
- Appearance of classic manifestations
  - Impairment of
    - Orientation
    - Memory
      - Recent >> remote
    - Judgement
    - Intellectual functions (comprehension, calculations, knowledge, learning, etc.)
    - Lability and shallowness of mood

**Late phase**
- Deterioration of alertness
  - Apathy progressing to stupor or coma
  - Deterioration in motility
  - Difficulty with speech and swallow
  - Incontinence
- May still be able to
  - Interpret and use basic body language
  - Enjoy sounds, tastes, smells, sights and touch

**Diagnosis of dementia**
1. Careful history and PE
2. Emphasis on MMSE, clock-drawing
3. Exclude depression, delirium, other “treatable causes” of dementia
**Case**

- A 78 year old woman is brought to the clinic because she forgets "everything", she can not perform even simple math calculation, she gets lost easily even around the neighborhood. Her regular doctor has concluded she has dementia. You are offering a second opinion.

Besides performing a complete history, physical and neurologic evaluation,
- Which are some reversible causes of dementia?
- What tests would you order?
- When would you order and RPR?, EEG?, and LP?

**Reversible Dementias**

<table>
<thead>
<tr>
<th>Medications</th>
<th>Depression</th>
<th>Metabolic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sedatives</td>
<td>- Brain lesions</td>
<td>- Thyroid disease</td>
</tr>
<tr>
<td>- Psychiatric</td>
<td>- Tumor</td>
<td>- Vit B12 deficiency</td>
</tr>
<tr>
<td>- Analgesics</td>
<td>- Subdural hematoma</td>
<td>- Hyponatremia</td>
</tr>
<tr>
<td>- Anticholinergics</td>
<td>- Chronic meningitis</td>
<td>- Hypercalcemia</td>
</tr>
<tr>
<td>Alcohol related</td>
<td>- Normal pressure hydrocephalus</td>
<td>- Hepatic and renal dysfunction</td>
</tr>
<tr>
<td>- Intoxication</td>
<td></td>
<td></td>
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<tr>
<td>- Withdrawal</td>
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</tbody>
</table>

**Laboratory Tests in the Diagnosis of Dementia**

(AAN Practice Parameter '01)

- CBC, electrolytes, glucose, BUN/creat
- LFTs, TFTs, ESR
- B12 level
- Depression screening
- CT or MRI scan

**Routine tests not recommended**

(AAN '01)

- RPR (unless evidence)
- SPECT
- Genetic testing (e.g. APOE)
- EEG
- LP (unless unusual factors- infection, hydrocephalus, etc.)
- Uncertain: PET (Medicare approved), other gene markers such as neuronal thread protein, CSF tau

**Etiologies of Dementia**

- Alzheimer’s disease
- Vascular (13-30%)
- Combined (10-15%)
- Parkinson’s Disease
- Huntington’s Disease
- Creutzfeldt-Jakob Disease
- Fronto-temporal dementias (Pick’s disease)
- Dementia with Lewy bodies
- HIV
- Tumor
- Head trauma
Alzheimer's Disease

- First described in 1907 by Alois Alzheimer
- In a 51 year old female with memory loss, disorientation and hallucinations
- Post-mortem studies characterized senile plaques and neurofibrillary tangles (NFTs) in the cerebral cortex
  - Senile plaques: extracellular accumulation of \( \beta \)-amyloid (A\(_{\beta}, 1-42 \))
  - NFTs: intracellular accumulations of hyperphosphorilated tau strands

Alzheimer's disease

Definition: NINCDS/ADRDA '84, DSM IV

- Acquired syndrome of memory and 2 other cognitive functions (aphasia, apraxia, agnosia, executive functions)
- Progressive
- Sufficient to affect daily life
- No alteration of consciousness
- Age of onset 40-90
- No other proved cause
- Correlation with pathology 80-100%

AD Epidemiology

- AD is the most common dementia (50-60% of dementia cases, another 15% mixed with vascular disease)
- AD affects ~4 million patients in U.S
- Projected: >14 million patients by 2050
- Costs: $90 to $100 billion/year
- Average cost of care: $50,000 per patient/year

10 Warning Signs of AD

(AAN Practice Parameter '01)

1. Memory loss that affects job skills
2. Difficulty performing familiar tasks
3. Problems with language
4. Disorientation to time and place
5. Decreased judgment
6. Problems with abstract thinking
7. Misplacing objects
8. Changes in mood or behavior
9. Changes in personality
10. Loss of initiative

Prevalence of AD Through 2030

Alzheimer’s Disease Prevalence

**Neuropathophysiology of AD: Overview**

- Amyloid plaque deposits and microglial activation
- Neurofibrillary tangles (NFTs)
- Neuronal cell loss
- Amyloid in vessels

**Cortical atrophy**

- Normal
- AD

**Amyloid Plaques and Microglial Activation**

This photo shows an Alzheimer amyloid plaque (white) surrounded by reactive microglial cells (black) sitting on top.

**Neurofibrillary Tangles**

This photo shows an Alzheimer amyloid plaque (brown) with many reactive microglial cells (black).

**Brain Hypofunction (PET)**

- Normal
- AD

**AD: Etiology**

- Genetics: chromosome 21, 1, 14 associated with early onset AD
- APO E4 associated with sporadic, late onset AD
- Amyloid hypothesis: APP, role of secretases
- Inflammation in plaques
- Vascular risk factors
Case

- A 62 year old man is brought to you because the family suspects he has “Parkinson’s disease”. Recently he wandered away from the house. Besides the mild parkinsonism easily identified by mere inspection, he has visual hallucinations of “little children running around the house”. On further questioning, he also has paranoid delusions. He has restless sleep. He is not oriented to time. You find that he has mild memory dysfunction and difficulty copying a pentagon. You witness occasional mild myoclonic jerks.

- What are some of your differential diagnoses?

Differential Diagnosis of AD

- Delirium: (drugs, toxins, systemic dz)
- Depression
- Metabolic (thyroid, calcium)
- Normal pressure hydrocephalus
- Subdural hematoma
- Tumor
- Infections
- Creutzfeldt-Jakob Dz
- Vascular dementia
- Dementia due to Parkinson’s disease
- Dementia with Lewy bodies
- Frontotemporal dementia

Lewy Body Dementia

- Mean age at onset 57 years, more common in men (1.7:1)
- Clinically a dementia with other features:
  - Fluctuating cognition or alertness
  - Recurrent visual hallucinations
  - Spontaneous features of parkinsonism
- Can have: falls, syncope, neuroleptic sensitivity, depression, RBD, delusions
- Rx: is difficult; selective neuroleptic therapy for neuropsychiatric symptoms; may attempt Sinemet®

Treatment of Dementia

Management of AD

1. Cholinesterase inhibitors
2. Psychotropic agents
3. Psychosocial intervention
4. Care giver support
Cholinesterase Inhibitors

- Improve global function and cognition
- Reduction in behavioral disturbances
- Temporary stabilization of ADLs
- Delay nursing home placement
- Reduced demand on caregiver time

Psychotropic Agents

- Behavioral management
  - Atypical antipsychotics
  - Anticonvulsants
  - Antidepressants

Care Giver Support

- Alliance with family
- Care giver spends most time with patient
  - Ensure adherence to management
- Care giver prone to depression and physical illness
- Families benefit from short educational programs

Caregiver Burden in AD

- Compared with non-caregiver controls matched by age, gender, race and marital status, caregivers of persons with AD or related disorders require
  - 46% more physician visits
  - 71% more prescribed medications
  - Higher diastolic blood pressure
  - Hypercoagulable state
  - Higher plasma norepinephrine

Important end-of-life issue!

- Discuss and document medical advance directives early in the course of the disease, when the patient is capable of making these decisions.

Questions?