Dementia
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To aid your study, the syllabus cross-references other Neuroscience Core IV lectures that provide supportive and complementary background information not repeated here. The lecture slides covering the information in the syllabus are indicated in the left-hand margin so you can follow along easily. The table and figures in the syllabus are intended as study aids; you will not be tested on their content.

OBJECTIVES
1. Describe how to recognize dementia and distinguish it from delirium, mild cognitive impairment and normal aging
2. Outline the methods and unique requirements of dementia evaluations
3. Identify the typical features and typical features of common and a few distinctive dementing diseases

RESOURCES
If there are discrepancies between this syllabus and other resources, including the lecture slide presentation, use the syllabus as your primary source of information. Test questions will be taken from the syllabus.

• Online: www.utahmemory.org (Center for Alzheimer’s Care, Imaging and Research); www.alzheimers.org (the Alzheimer’s Disease Education and Referral Center, NIH), includes the 2005-2006 Progress Report on Alzheimer’s Disease with summary of current knowledge about Alzheimer’s disease and recent research

SYLLABUS CONTENTS / TOPICS
• Recognition of Dementia
• Dementia Evaluations
• Common Neurological Dementing Disorders
• Summary: Important Facts About Dementia

RECOGNITION OF DEMENTIA
Dementia: A decline of intellectual function from previous level of performance sufficient to impair daily activities in someone who is alert and cooperative

• Intellectual function denotes two or more cognitive domains
• Static or progressive, acute or chronic, reversible or irreversible
• Can occur at any age, but much more common in the elderly
• Distinguish from delirium, a disorder of attention with fluctuating alertness and mild cognitive impairment (MCI), where impairment is insufficient to impair daily activities

Mild Cognitive Impairment: Objective evidence of an acquired deficit in one or more cognitive domains insufficient to impair everyday activities

Delirium: A disorder of attention fluctuating in intensity throughout the day causing changing levels of consciousness, perceptual disturbance, altered psychomotor activity, disorientation and memory impairment.
• Use **triggers** to identify dementia and its cause early, when treatments are most effective:
  
  o Difficulty providing coherent history or following instructions during examination
  
  o Failing to keep appointments, take medications as directed, or depending on others
  
  o Delirium or “confusion” from a medication, medical illness, or surgery

**Dementia Evaluations**

**Initial Dementia Assessment**

**Purpose: Determine whether a dementing disease is likely**

1. Evaluate when there is a complaint or trigger

2. Obtain a focused history from the patient and at least one other knowledgeable informant.

3. Patients may not recognize their deficits or have difficulty remembering their symptoms.

4. Consider the type of symptoms. Is there memory loss, impaired attention, or something else?

5. Evaluate the onset and course of symptoms. Does their onset correlate with a change in mood, sleep or medication use? Depression alters attention, concentration and motivation. The depressed patient often denigrates abilities. It is easy for a physician to confuse depression and dementia. Sleep disorders and medications with CNS effects, especially hypnotic drugs, impair memory performance. Medications are most frequent reversible cause of dementia. If possible, discontinue CNS active medications. Remember that the elderly metabolize many drugs differently and are particularly susceptible to medication side effects.

6. Family history of a dementing disease may increase risk and warrant greater concern

7. Assess vision and hearing; visual impairment and hearing loss are very common in the elderly, particularly in those over 90, and may explain poor cognitive test performance.

8. Look for evidence of medical illnesses

9. Perform a careful neurological examination; most common causes of dementia are neurological diseases.

10. Perform mental status exam: document both abilities and deficits; is the complaint confirmed on exam?

11. Assess whether there is any functional impairment. If there is difficulty with everyday activities, how much is it due to cognitive problems, lack of motivation, or physical disability.

   • If exam shows no cognitive impairment or functional loss, despite a complaint, you can reassure the patient. However, you need to re-evaluate in 6-12 months, because patients and families may be more sensitive to changes than findings at a clinic visit.
• Consider the possibility of multiple diseases contributing to cognitive impairment. With increasing age, “mixed dementia” is more common, e.g. Alzheimer’s with stroke.

Figure. Flow chart for recognition and initial assessment of Alzheimer’s disease and related dementias

- Symptoms possibly indicating dementia (“triggers”)
- Conduct initial clinical assessment
  - Focused history
  - Focused physical exam
  - Functional status
  - Mental status (consider confounding and comorbid conditions)
- Delirium or depression present?
  - Yes
    - Evaluate, treat, and reassess
  - No
- Interpret results of functional and mental status tests (consider confounding factors)
- No
- Yes
- 1. Result normal: mental status normal, no functional losses
  - Reassure (suggest followup in 6–12 months)
  - Remaining concern?
    - Yes
      - Consider referral for second opinion or further clinical evaluation
    - No
      - Evidence of dementia?
        - Yes
          - Conduct further clinical evaluation or refer for second opinion
        - No
          - Follow up on nondementia problems
- 2. Result abnormal: mental status impaired, functional losses present
- 3. Result mixed:
  - 3a. Mental status impaired, no functional losses
    - Refer for neuropsychological and, as indicated, neurological or psychiatric evaluation
  - 3b. Mental status normal, functional losses present
    - Refer for neurological or psychiatric and, as indicated, neuropsychological evaluation

**FULL DEMENTIA ASSESSMENT**

**PURPOSE: DETERMINE THE SPECIFIC CAUSE OF DEMENTIA**

1. Determine onset of symptoms. Did symptoms come on suddenly or develop insidiously?

2. What has been the course of symptoms? Have symptoms been stable, step-wise, progressive, or only consist of distinct episodes?

3. What was the first symptom? Is this or another symptom now most prominent? and when were they noticed?

4. Determine onset and course of symptoms. What were first symptoms and when were they noticed? Did symptoms come on suddenly or develop insidiously? Have symptoms been stable, step-wise, progressive, or only consist of distinct episodes?

5. Perform mental status exam to document both abilities and deficits; consider each major cognitive domain (see below).

6. Perform a careful neurological examination; most common causes of dementia are neurological diseases. Look for localizing neurological signs such as focal weakness, rigidity, ataxia, asymmetric or abnormal reflexes.

7. Look for medical illnesses; they can cause dementia or worsen an underlying dementia. Screening laboratory blood tests assist in this search.

8. Brain imaging can identify evidence of neurological disease. Sometimes lumbar puncture is needed to identify cerebrospinal fluid abnormalities. EEG and skin or brain biopsy may be necessary in some cases.

**Assessing Cognitive Domains:**

1. Four major localizable cognitive domains of memory, language, visuospatial processing, and executive function (Table 1) should be considered in dementia evaluations.

2. Other parts of mental status exam, such as affect and alertness, are important and should be described, but are not localizable cognitive domains. Orientation to person, time and place are not localizable or reflect function of a specific region of the cerebral cortex.

3. There are many more specific cognitive abilities such as reading, writing, and calculation that are localizable, but relevant only in special circumstances.

4. Bedside cognitive assessment uses clinical rating scales (such as MMSE or clock-drawing) or can be interactive and adjusted based upon prior ability

5. Neuropsychological testing uses a battery of standardized tests performed with
consistent rules of administration in a controlled setting to provide objective and quantifiable measure of cognitive performance

**Table: Four Major Localizable Cognitive Domains**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Deficit</th>
<th>Localization</th>
<th>Bedside Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>Amnesia, often more noticeable to others</td>
<td>Bilateral, hippocampus, thalamus, cerebral hemispheres</td>
<td>Recall of 3 words after a 5 minute delay</td>
</tr>
<tr>
<td>Language</td>
<td>Aphasia</td>
<td>Dominant hemisphere</td>
<td>Name objects, verbal fluency</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>Apraxia</td>
<td>Non-dominant hemisphere</td>
<td>Difficulty mimicking movements, copying drawings</td>
</tr>
<tr>
<td>Executive function</td>
<td>Impaired judgment, change in personality and behavior</td>
<td>Frontal lobes</td>
<td>Appropriateness during interaction, attending to task</td>
</tr>
</tbody>
</table>

**Unique Aspects of Dementia Evaluations:**

1. Knowledgeable informants are needed to assure an accurate history. These individuals also are important to help carry out treatment recommendations.

2. Physicians need to establish a “therapeutic triad” involving the patient and caregivers. This is different than pediatrics where parents are addressed primarily. In dementia care, patients need to be addressed and involved in care, while also involving family members and other caregivers simultaneously - a difficult and valuable skill.

3. It is important to evaluate the network of care providers to adequately support the patient. All family members should be involved whenever possible. Family members shouldn’t be expected to provide all care on their own. Community-based services, such as the Alzheimer’s Association, adult day-care, housekeeping assistance and respite care are invaluable.

4. Patients with memory loss (and their caregivers) naturally tend to withdraw from activities and their social contacts. Studies show less than 10% get out of the house daily. Physicians should encourage social involvement, mental engagement, and regular physical activity.

5. Education is important for self-management of all chronic diseases. However, in dementia education needs to involve both patients and caregivers. Providing care for patients with memory loss and dementia requires different skills than those needed for child care or other chronic diseases.
Regular Physician Visits are Needed for Dementia Care:

1. Many dementing diseases are progressive. Consequently, symptoms change and treatment must be modified to address these changes.

2. Early interventions are most effective. This is particularly true for behavioral problems. Behavior disturbance may be due to insufficient supervision, caregiver stress, medical complications, or disease progression. Regular visits are needed to distinguish these causes and detect them before they become crises.

3. Monitor not just cognition, but also nutrition, physical health, and caregiver status. These are important indices of effective treatment.

4. Regular physician support is important in care. Be proactive rather than reactive in dementia care. This can make a major difference in costs of care.

COMMON NEUROLOGICAL DEMENTING DISORDERS

Alzheimer’s Disease

- Most common cause of dementia in the elderly
- Insidious onset, gradual, progressive course
- Memory loss usually first and most prominent symptom
- No focal weakness or sensory loss; gait normal and continent until late in the illness
- Temporoparietal > frontal hypometabolism with sparing of primary motor and sensory cortex

Typical Course of Alzheimer’s Disease

Note that on average in AD MMSE declines 3 points/yr and follows this time course, but there is much individual variation
NINCDS-ADRDA criteria, validated

- **Definite AD**  clinical features **and** typical pathology  100% accurate
- **Probable AD**  typical, uncomplicated  85-95% certain
- **Possible AD**  atypical or complicated by other illnesses  65-75% certain

**Note:** Clinical information alone can only lead to a diagnosis of probable or possible AD (this is not the same as probably or possibly AD!!). These diagnostic categories are based upon findings during the full dementia evaluation, so patients generally do not change from possible to probable or from probable to possible once a diagnosis is made.

**Risk factors:**

- Age, increases dramatically with age, prevalence >65 is 5%, >85 is 40%
- Down's syndrome (trisomy 21)
- 2>1>0 apolipoprotein E4 alleles (apoE types are apoE3, apoE4, & apoE2)
- Low educational and occupational attainment
- Family history of dementia, especially if AD confirmed at autopsy

- **Familial AD:**
  - Autosomal dominant, about 10% of all AD
  - Genetic mutations responsible for late-onset (age >65) AD unknown
  - Early-onset (age <65) familial AD can be caused by:
    - presenilin 1 (PS1) mutation (about 50%)
    - presenilin 2 (PS2) mutation (rare),
    - amyloid precursor protein mutation (APP, rare)
    - and other unknown mutations
    - Mutations cause excess production of abeta 1-42 (found in plaques) relative to abeta 1-40 (found mostly in amyloid angiopathy)

**Current Treatment of AD:**

1. Cholinesterase inhibitors: offsets selective loss of cholinergic neurons, which originate in the nucleus basalis of Meynart
2. Low affinity, non-competitive NMDA glutamate receptor antagonist, memantine, believed to offset glutamate neurotoxicity
3. High dose vitamin E (2000 IU/d): shown to delay progression of moderate AD, acting as an anti-
oxidant and most likely offsetting the inflammatory response around neuritic plaques

- **Promising New AD Treatment Strategies:**

1. Future treatments likely to target beta-amyloid processing, so that less abeta is produced from APP.

2. Additional strategies are under investigation that reduce total abeta or amyloid plaque formation by inhibiting abeta aggregation or increasing clearance of abeta from the brain.

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**Schematic of steps in the activation of the membrane protein presenilin (PS1) as an enzyme and the subsequent two alternative pathways for amyloid precursor protein (APP) processing involving alpha or beta secretases and PS1. The first pathway produces the potentially neurotoxic abeta protein of Alzheimer’s disease.**
**Frontotemporal Dementia**

- Insidious onset of progressive dementia with disturbing behavior and speech problems most prominent; memory impairment and apraxia often less evident
- Speech: perseveration, decreased word fluency, can’t understand word meaning (semantic dementia)
- Often exhibit prominent behavioral symptoms such as any combination of:
  - Personal neglect, emotional indifference, inertia, lack of spontaneity
  - Lack of social tact, impulsivity, disinhibited behavior (e.g., unrestrained sexuality, inappropriate jocularity)
  - Repetitive stereotyped and bizarre or ritualistic behavior
- May be associated with motor neuron disease
- More frequent at younger ages, AD and FTD incidence about same if age <60
- Focal atrophy, hypometabolism involving frontal and anterior temporal cortex
- Imbalance of tau isoforms causing tau inclusions OR ubiquitin inclusions
- About 10-20% familial, Frontotemporal Dementia with Parkinsonism Linked to Chromosome 17 (FTDP-17) either due to mutation in either: tau or progranulin (have ubiquitin inclusions)
  - Tau gene, most have an intronic mutation causing 4 repeat or 3 repeat tau inclusions
  - Progranulin gene, a nerve growth factor for frontal cortex, causing ubiquitin inclusions

**Dementias with Parkinsonism**

**Dementia with Lewy Bodies (DLB):**

- Dementia with spontaneous parkinsonism
- Visual hallucinations
- Unexplained fluctuations in attention and alertness
- Temporoparietal and occipital hypometabolism

**Parkinson's Disease with Dementia:**

- Onset of motor symptoms first, especially tremor
- Dementia affects 30% of patients with PD
- More common with increasing age of patient
- Treatment of motor symptoms can worsen or improve dementia symptoms
At autopsy such patients can have DLB, PD only, or PD with AD

**Progressive Supranuclear Palsy:**
- Supranuclear gaze palsy (impaired voluntary > involuntary eye movements)
- Pseudobulbar palsy with dysarthria and choking
- Ataxic gait and falling; limb and axial rigidity
- Insidious onset, progressive frontotemporal dementia
- 4R tau neurofibrillary tangles, primarily subcortical

**Corticobasal Degeneration (CBD):**
- Sporadic, onset age >55
- Asymmetric rigidity
- Profound asymmetric apraxia with alien hand
- Insidious onset, progressive dementia
- Neuronal loss in cortex and basal ganglia
- Achromatic 4R tau neuronal inclusions

**Vascular Dementia**
- Sudden onset, stepwise course
- Focal motor, sensory, and reflex findings
- Cognitive impairments predominantly in one hemisphere
- Seizures, gait impairment and urinary incontinence early in the illness
- Stroke on CT and MRI

**Pathophysiology of Vascular Dementia:**
- Severity of dementia related to extent of functional impairment of association cortex (infarcted tissue + deafferentation)
- Multiple strokes have a synergistic effect
- Lacunar infarcts may cause symptoms of frontotemporal dementia
- May have no focal sensory or motor findings if: 1) patient has recovered from motor/sensory deficits while cognitive changes persist, OR 2) strokes are in areas that only affect cognition, not motor or sensory areas or tracts
Treatment of Vascular Dementia:

- This dementia is preventable! Treat underlying cause to prevent recurrent stroke.
- Risk factors same as for stroke and should be treated: hypertension, smoking, heart disease (particularly valvular heart disease and atrial fibrillation, hypercholesterolemia, hypercoaguable states)

**Creutzfeldt-Jakob Disease**

- Rapidly progressive (course usually < 1 year)
- Often begins with focal symptoms, such as ataxia or blindness
- Startle myoclonus, rigidity
- Progressive, periodic sharp wave discharges on EEG
- Causes focal hyperintensity in diffusion-weighted MRI
- Transmissible by CNS tissue or blood
- Caused by a prion (self-replicating protein) that is destroyed by chlorox and NaOH, but not formaldehyde or alcohol
- Familial in about 10% due to a mutation of prion protein
- Familial CJD may have atypical symptoms such as prolonged course or normal EEG. In these circumstances it may be an Alzheimer mimic.

**SUMMARY: IMPORTANT FACTS ABOUT DEMENTIA**

- Dementia is a symptom, not a diagnosis
- Dementia is a multi-focal disorder of higher cognitive abilities, affecting some cognitive domains more than others, depending upon the cause of dementia
- Dementia may not be immediately apparent and intrudes on all kinds of medical care
- Crises in care can be prevented by evaluating and supporting caregivers and helping them plan for future needs and the unexpected
- Treatment of dementia depends upon its cause
- Some dementias can be prevented including vascular dementia (prevent stroke) and by early treatment of medical illnesses
- Drug and non-drug treatments often help dementia; more effective drugs are in development
- Dementia often has multiple causes, particularly in the elderly