ALZHEIMER’S DISEASE

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Topics Covered

• Demography
• Clinical manifestations
• Pathophysiology
• Diagnosis
• Treatment
• Future trends
Prevalence and Impact of AD

- AD is the most common cause of dementia in people 65 years and older
- Affects 10% of people over the age of 65 and 50% of people over the age of 85
- Approximately 4 million AD patients in the United States
- Annual treatment costs = $100 billion
- AD is the fourth leading cause of death in the United States
- The overwhelming majority of patients live at home and are cared for by family and friends

DIFFERENTIAL DIAGNOSIS

• Alzheimer’s disease
• Vascular (multi-infarct) dementia
• Dementia associated with Lewy bodies
• Delirium
• Depression
• Other (alcohol, Parkinson's disease [PD], Pick’s disease, frontal lobe dementia, neurosyphilis)
Delirium and dementia often occur together in older hospitalized patients; the distinguishing signs of delirium are:

- Acute onset
- Cognitive fluctuations over hours or days
- Impaired consciousness and attention
- Altered sleep cycles
VASCULAR DEMENTIA

• Development of cognitive deficits manifested by both
  • impaired memory
  • aphasia, apraxia, agnosia, disturbed executive function

• Significantly impaired social, occupational function

• Focal neurologic symptoms & signs or evidence of cerebrovascular disease

• Deficits occur in absence of delirium
Depression vs Dementia

- The symptoms of depression and dementia often overlap; patients with primary depression:
  - Demonstrate ↓ motivation during cognitive testing
  - Express cognitive complaints that exceed measured deficits
  - Maintain language and motor skills
Projected Prevalence of AD

4 Million AD Cases Today—
Over 14 Million Projected Within a Generation

The Progress of Alzheimer’s Disease

- Early diagnosis
- Mild-moderate
- Severe

Cognitive symptoms

Loss of ADL

Behavioral problems

Nursing home placement

Death

MMSE score vs. Years
Alzheimer’s Disease Progresses Through Distinct Stages

**Stage**

- **Mild**
  - Memory loss
  - Language problems
  - Mood swings
  - Personality changes
  - Diminished judgment

- **Moderate**
  - Behavioral, personality changes
  - Unable to learn/recall new info
  - Long-term memory affected
  - Wandering, agitation, aggression, confusion
  - Require assistance w/ADL

- **Severe**
  - Gait, incontinence, motor disturbances
  - Bedridden
  - Unable to perform ADL
  - Placement in long-term care needed

**Symptoms**

Dementia/Alzheimer’s
WHAT IS DEMENTIA?

• An acquired syndrome of decline in memory and other cognitive functions sufficient to affect daily life in an alert patient

• Progressive and disabling

• NOT an inherent aspect of aging

• Different from normal cognitive lapses
Normal Lapses

- Forgetting a name
- Leaving kettle on
- Finding right word
- Forgetting date or day

Dementia

- Not recognizing family member
- Forgetting to serve meal just prepared
- Substituting inappropriate words
- Getting lost in own neighborhood
Normal Lapses

- Trouble balancing checkbook
- Losing keys, glasses
- Getting blues in sad situations
- Gradual changes with aging

Dementia

- Not recognizing numbers
- Putting iron in freezer
- Rapid mood swings for no reason
- Sudden, dramatic personality change
RISK FACTORS FOR DEMENTIA

• Age

• Family history

• Head injury

• Fewer years of education
THE GENETICS OF DEMENTIA

- Mutations of chromosomes 1, 14, 21
- Rare early-onset (before age 60) familial forms of dementia
- Down syndrome

- Apolipoprotein E4 on chromosome 19
- Late-onset AD
  - APOE*4 allele ↑ risk & ↓ onset age in dose-related fashion
  - APOE*2 allele may have protective effect
PROTECTIVE FACTORS UNDER STUDY

• Estrogen replacement therapy after menopause

• NSAIDs

• Antioxidants
LEWY BODY DEMENTIA

- Dementia
- Visual hallucinations
- Parkinsonian signs
- Alterations of alertness or attention
Pathology of AD

• There are 3 consistent neuropathological hallmarks:
  – Amyloid-rich senile plaques
  – Neurofibrillary tangles
  – Neuronal degeneration

• These changes eventually lead to clinical symptoms, but they begin years before the onset of symptoms
β-amyloid Plaques

Immunocytochemical staining of senile plaques in the isocortex of a brain of a human with AD (anti-amyloid antibody)
Neurofibrillary Tangles

Immunocytochemical staining of neurofibrillary tangles in the isocortex of the brain of a human with AD (anti-tau antibody)
Cholinergic Hypothesis

- Acetylcholine (ACh) is an important neurotransmitter in areas of the brain involved in memory formation
- Loss of ACh activity correlates with the severity of AD

Acetylcholinesterase Inhibitors

• Drugs used to treat Alzheimer’s disease act by inhibiting acetylcholinesterase activity

• These drugs block the esterase-mediated metabolism of acetylcholine to choline and acetate. This results in:
  – Increased acetylcholine in the synaptic cleft
  – Increased availability of acetylcholine for postsynaptic and presynaptic nicotinic (and muscarinic) acetylcholine receptors
Acetylcholinesterase Inhibition

Acetylcholine (ACh) is released from the presynaptic nerve terminal. It binds to postsynaptic muscarinic receptors, activating them.

Acetylcholinesterase (AChE) is an enzyme found in the postsynaptic nerve terminal that breaks down ACh into choline and acetic acid.

ASSESSMENT: HISTORY

(1 of 4)

• Ask both the patient & a reliable informant
• about the patient’s:

• Current condition
• Medical history
• Current medications & medication history
• Patterns of alcohol use or abuse
• Living arrangements
ASSESSMENT: PHYSICAL
(2 of 4)

- Examine:
  - Neurologic status
  - Mental status
  - Functional status

- Include:
  - Quantified screens for cognition
    - e.g., Folstein’s MMSE, Mini-Cog
  - Neuropsychologic testing
ASSESSMENT: LABORATORY (3 of 4)

• Laboratory tests should include:

  • Complete blood cell count
  • Blood chemistries
  • Liver function tests
  • Serologic tests for:
    - Syphilis, TSH, Vitamin B$_{12}$ level
ASSESSMENT: BRAIN IMAGING (4 of 4)

• Use imaging when:
  • Onset occurs at age < 65 years
  • Symptoms have occurred for < 2 years
  • Neurologic signs are asymmetric
  • Clinical picture suggests normal-pressure hydrocephalus

• Consider:
  • Noncontrast computed topography head scan
  • Magnetic resonance imaging
  • Positron emission tomography
Treatment of Alzheimer’s Disease

- Prevalence: 4,523,100
- Diagnosed: 2,261,600
- Treated: 904,600
- Treated with AChEIs: 543,800

*Any drug treatment, not limited to acetylcholinesterase inhibitors.

Primary goals: to enhance quality of life & maximize functional performance by improving cognition, mood, and behavior

- Nonpharmacologic
- Pharmacologic
- Specific symptom management
- Resources
NONPHARMACOLOGIC

• Cognitive enhancement
• Individual and group therapy
• Regular appointments
• Communication with family, caregivers
• Environmental modification
• Attention to safety
**PHARMACOLOGIC**

- Cholinesterase inhibitors: donepezil, rivastigmine, galantamine
- Other cognitive enhancers: estrogen, NSAIDs, ginkgo biloba, vitamin E
- Antidepressants
- Antipsychotics
SYMPTOM MANAGEMENT

• Sundowning
• Psychoses (delusions, hallucinations)
• Sleep disturbances
• Aggression, agitation
• Hypersexuality
RESOURCES FOR MANAGING DEMENTIA

• Attorney for will, conservatorship, estate planning

• Community: neighbors & friends, aging & mental health networks, adult day care, respite care, home-health agency

• Organizations: Alzheimer’s Association, Area Agencies on Aging, Councils on Aging

• Services: Meals-on-Wheels, senior citizen centers
SUMMARY (1 of 2)

• Dementia is common in older adults but is NOT an inherent part of aging

• AD is the most common type of dementia, followed by vascular dementia and dementia with Lewy bodies

• Evaluation includes history with informant, physical & functional assessment, focused labs, & possibly brain imaging
Primary treatment goals: enhance quality of life, maximize function by improving cognition, mood, behavior

Treatment may use both medications and nonpharmacologic interventions

Community resources should be used to support patient, family, caregivers
Future Trends

• Alzheimer’s as a multifactorial syndrome
• Pendulum of history
• Vaccine
• Genetic therapy