The Diagnosis, Treatment, and Management of Dementia

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Talk Outline

- Prevalence of dementia
- Diagnosis of dementia
  - Diagnostic criteria
  - Diagnostic work-up
- Alzheimer’s, Lewy body, Parkinson’s dementia
- Treatment of dementia
- What’s new in risk factors?
Dementia: Common, Expensive, Treatable

- 11% of people > age 65
- 32% of people > age 85
- 5.4 million Americans over age 65
  - 200,000 under age 65
- 6th leading cause of death
- A third of all seniors who die have dementia
- $200 billion in 2012

Alzheimer's Assoc 2014 Alzheimer's disease facts & figures

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Dementia: Common, Expensive, Treatable

- 25.6 million cases in 2010 World Health Organization (WHO)
  - Incidence doubles every 20 years
  - 115.4 million cases in 2050
- Aging is single greatest risk factor

The Silver Tsunami

By 2050, People Age 65 and Older Will Equal 20% of the Population

U.S. Population (and Forecast) by Age Category and Gender

Dementia Diagnosis

Diagnostic criteria
Office-based cognitive tests
Questions to ask
Laboratory & Neuroimaging
Dementia: Outdated Classification

- Cortical Dementia
  - Alzheimer's disease
  - Frontotemporal dementia
- Subcortical Dementia
  - Vascular dementia
  - Dementia with Lewy bodies
  - Parkinson's disease
  - Progressive supranuclear palsy
  - Normal pressure hydrocephalus

Dementia: DSM-IV Criteria

A. Impairment in memory

B. At least 1 of the following:
  - Aphasia
  - Apraxia
  - Agnosia
  - Executive function problems

C. Memory impairment and intellectual impairment significantly interfere with work, social activities, or relationships

D. Disturbance does not occur exclusively during delirium
The Dementia Syndrome

- Memory deficit is the main feature
- Other cognitive deficits
  - Attention
  - Executive function
- Abstract thinking
- Calculation
- Personality disturbances
- Behavioral disorders
- Neurologic deficits

Dementia: DSM-V (May 2013)

- ‘Dementia’ replaced by:
  - Minor Neurocognitive Disorder
  - Equivalent to Mild Cognitive Impairment (MCI)
  - Major Neurocognitive Disorder
  - Equivalent to Dementia
- Reason: ‘Dementia’ has been stigmatized
- Not endorsed by the American Neurological Association, American Geriatrics Society, or Alzheimer’s Association

NIA/AA Criteria: MCI Due to AD

- Mild Cognitive Impairment (MCI)
- Clinical and cognitive criteria
  - Concern of change in cognition (patient, informant of clinician)
  - Impairment in one or more cognitive domains, including memory
  - Independent in functional abilities
  - Not demented


NIA/AA Criteria: All-cause Dementia

- Decline from prior level of function
  - Function at work or social activities impaired
- Cognitive impairment
  - History from patient + informant
  - Cognitive testing (office or neuropsych)
- Impairment of 2 or more cognitive domains
  - Memory
  - Reasoning/judgment
  - Visuospatial ability
  - Language
  - Personality, behavior
  - or comportment

NIA/AA Criteria: Alzheimer’s disease

- Satisfies criteria for All-cause dementia
- Insidious onset over months to years
- Progressive cognitive impairment
  - Amnestic presentation (vast majority)
  - Non-amnestic presentation (language, visuospatial, executive dysfunction)
- Exclusionary criteria:
  - Vascular/Lewy body/Frontotemporal dementia, etc.


Continuum of Memory Loss
Dementia: Etiology

- Alzheimer’s Disease 70%
- Vascular Dementia 20%
- Lewy Body/Parkinson’s Disease 5%
- Others 5%

Case of Patient A

- 78 year old M businessman who complains of forgetfulness
- Lifelong smoker, hypertension, diabetes
- In past 3 years, has needed to write down appointments and take notes in meetings
- Denies forgetting something important
- On testing, only problem is with memory

Diagnosis?
Case of Patient A

A. Mild cognitive impairment, amnestic
B. Mild cognitive impairment, nonamnestic
C. Alzheimer’s disease
D. Vascular dementia
E. Lewy body dementia
F. Parkinson’s dementia
Mild Cognitive Impairment, Amnestic

- 70% progress to Alzheimer’s disease
  - Rate of progression: 15% per year
- 30% stable or improve
- How can one prevent progression?

- 769 patient with MCI followed for 3 years
- Donepezil 10 mg, Vitamin E 2000 IU, or placebo
- Results:
  - Donepezil group with lower rate of progression only in first year
  - Vitamin E had no effect
  - No differences in probability of progression to AD over 3 years

NEJM 2005;352:23
MCI is NOT:

- Age-associated memory impairment (AAMI)
  - Generalized slowness in storing, processing and recalling new information
    - Difficulty in remembering names and words
    - Difficulty with memory for intentions
  - Decline in cognition relative to past performance but within normal range for age
  - Due to physiological changes in aging brain

Risk Factors for Dementia

- Older age
- Family history
- Genetic factors (ApoE4)
- Head trauma
- Medical comorbidity
Questions to Ask: NW-CALMS

1. What is the Nature of the change in behavior/cognition?
2. When was the change in behavior/cognition first observed?
3. What is the Course of the change?
4. Any change in performance of ADLs/IADLs?
5. Any recent changes in Life situation, Mood, Status of health?

Mini-Cog

- Very brief cognitive screening instrument
- 3-item recall test & clock-drawing test
- Normal clock: Correct configuration/time
- Twice as fast as the MMSE
- Less affected by ethnicity, language, education, socioeconomic status

Mini-Cog: Instructions

1. “Remember the following words:”
   Apple           Table           Penny
2. “Inside the circle draw in the hours of the clock and set the hands to ten past eleven”
3. “Repeat the three words I asked you to remember.”


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Mini-Cog: Interpretation

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MINI-COG
  Recall = 0
  Clock Abnormal
    DEMENTED

  Recall = 3
  Clock Normal
    NON-DEMENTED

Recall = 1-2
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Montreal Cognitive Assessment (MoCA)

- Screening tool for cognitive impairment
- Takes 10 minutes to administer
- Assesses several domains: memory, language, executive function, etc.
- Total 30 points, cut off: 26
- Available in different languages
- Free pdf download: www.mocatest.org

Diagnostic Tests for Memory Problems

- Routine Laboratory Tests (American Academy of Neurology Practice Guidelines)
  - **Recommended**
    - TSH
    - Vitamin B12
  - **Not recommended**
    - Syphilis serology
    - CBC, electrolytes, BUN, LFTs, calcium

Knopman DS et al. Neurology 2001; 56:1143
Diagnostic Tests for Memory Problems

- **Neuroimaging Test** (American Academy of Neurology Practice Guidelines)
  - Recommended:
    - CT Scan or
    - MRI
  - Not Recommended
    - Positron Emission Tomography (PET) Scan
    - Single Photon Emission Tomography (SPECT) Scan
    - Electroencephalograph (EEG)

What’s New in Dementia Diagnosis? Biomarkers

- **Structural MRI/CT**
  - Look for: atrophy of medial temporal lobe, anterior temporal and parietal cortex
- **CSF Aβ, p-tau, total tau**
  - Look for: decreased Aβ, increased p-tau/total tau
  - Not for dementia diagnosis, but to know if AD
- **FDG-PET**
  - Look for: decreased metabolism in temporal and parietal lobes
  - Distinguish between AD and frontotemporal dementia
A-β PET Scan

- Flurine-based compound
- Preliminary FDA approval
- Detects AD pathophysiology by binding to Aβ
- Caution: Will detect AD pathology in asymptomatic patients who may not develop dementia for 10-15+ years
- Clinically not useful currently, as no disease-modifying treatment available

Case of Patient B

- 78 year old female
- Started misplacing things 6 years ago
- Progressively become more repetitive with questions
- Got lost while walking home from market
- Interview reveals word-finding difficulty
- Remembers details of early life
- Mini-cog: Remembered 2 of 3 words; could not set the hands of the clock

Diagnosis?
Case of Patient B
A. Mild cognitive impairment, amnestic
B. Mild cognitive impairment, non-amnestic
C. Alzheimer’s disease
D. Vascular dementia
E. Lewy Body dementia
F. Parkinson’s dementia
Treatment of Alzheimer’s Dementia

- **Cholinesterase Inhibitors**
  - AD causes decrease in acetylcholine production
  - Inhibits acetylcholinesterase at the synaptic cleft
  - Tacrine (Cognex)
    - First FDA-approved AD drug
    - 10-40 mg QID
    - Causes Hepatotoxicity

Treatment of Alzheimer’s Dementia

- **Donepezil**
  - Once a day dosing & well-tolerated
  - Cholinergic side effects in 20% of patients
  - FDA-approved for mild to severe AD
  - Available in orally-dissolving tab
  - Dosing: 5 mg X 4 wks → 10 mg QD
Treatment of Alzheimer’s Dementia

- Rivastigmine
  - FDA-approved for mild to moderate AD
  - 1.5 mg BID → 6 mg BID
    (1.5 mg/dose increments Q2-4wks)
  - Efficacy comparable to donepezil but GI side effects may be higher
  - Available in patch 4.6 mg or 9.6 mg/24h

- Galantamine
  - FDA-approved for mild to moderate AD
  - Dose: 8mg →16mg → 24 mg QD (every 4 weeks)
  - Similar efficacy to donepezil but may have more GI side-effects
  - Least expensive
Treatment of Dementia

- Huperzine A (Cerebra)
  - Nutritional product
  - Acetylcholinesterase inhibitor + NMDA – receptor antagonist
  - Chinese clinical trials: effective in treatment of AD
  - US clinical trial did not show difference from placebo

Cholinesterase Inhibitors: The Evidence

- Improved cognition, activities of daily living, and global function in mild to moderate disease
  - Neurology 2000;54:2261
  - BMJ 1999;318:633
  - Neurology 1998;50:136
- Improved cognition and behavior in mild to moderate & moderate to severe disease
  - Neurology 2001;57:613
  - Neurology 2000;54:2269
- Reduced behavioral disturbances in mild to moderate disease
  - Am J Psychiatry 2004;161:532
Which of the following is **NOT** a known adverse reaction to acetylcholinesterase inhibitors?

A. Urinary obstruction  
B. Bradycardia  
C. GI Bleed  
D. Constipation  
E. Vivid dreams
Cholinesterase Inhibitor Side Effects

- **Gastrointestinal**
  - Anorexia, nausea/vomiting, diarrhea
  - Take with food
- **Vivid dreams**
  - Take in AM
- **Cholinergic side effects**
  - Bradycardia
  - Muscle cramps, rhinorrhea, increased saliva

Treatment Expectation

- **MODEST!**
  - Average MMSE change 0.8
  - May become less repetitive with questions
  - Keep track of conversations
  - Less misplacing things
  - Greater social engagement
Expected Responses

- 25–30% - improvement equivalent to 1 year reversal of symptoms
- 50–60% - improvement equivalent to 6 months reversal of symptoms
- 10–15% - improvement equivalent to <6 months reversal or no improvement

High-dose Donepezil

- Donepezil (Aricept) 23 mg QD pill
- FDA-approved
- Should we use this for moderate to severe dementia patients?
High-dose Donepezil

- 1467 patients (MMSE 0-20) on donepezil 10 mg
- Randomized to 23 mg or continue with 10 mg for 24 weeks
- Cognition: Improved (Severe Impairment Battery)
- Clinician’s impression of change: no difference
- Withdrawal from study: 30% vs 18%
- Treatment-emergent adverse effects: 74% vs 64%


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High-dose Donepezil

- Should we use this for our moderate to severe dementia patients?
  - Consider selectively in patients with moderate to severe AD if cognitive improvement would improve quality of life
  - For most patients, side-effects outweigh modest benefits
Treatment of Alzheimer’s Dementia

- Memantine
  - Blocks N-methyl-D-acetyl (NMDA) receptors from overstimulation by glutamate
  - FDA-approved for moderate to severe AD
  - Useful as a single or add-on therapy
  - Dose: 10 mg bid (5 mg increments every week)

Memantine for Moderate to Severe AD

- Improvement in cognition, function, behavior with memantine+donepezil vs. donepezil

  JAMA 2004;291:317

- Improvement or less decline in cognition, activities of daily living, global change, and reduced care dependence

  NEJM 2003;348:1333
Memantine for Vascular Dementia

- 321 patients (MMSE 12-20) for 28 weeks
- Memantine 10 mg bid vs. placebo
- Improvement in ADAS-Cog, MMSE, behavior

Dementia Treatment: Summary

- Medication review and stop anticholinergic and non-essential medications
- Check TSH, Vit B12, and CT/MRI (?)
- Neuropsychological testing (?)
- Medications (i.e. donepezil, rivastigmine, galantamine, memantine)
- Ensure home safety
Clinical Trials for Dementia

- Nerve Growth Factor Gene Transfer
- Other immunotherapies
  - Vaccines
  - Antibodies (e.g., IvIg)
- Gamma Secretase Inhibitors/modulators
- Study of the medical food Axona
- Inhaled Insulin
- Exercise

Case of Patient C

- 78 year old M complains of forgetfulness
- Memory problems began 4 years ago
- In the past 2 years, developed shuffling gait
- On examination, cogwheeling rigidity and pill-rolling tremor

Diagnosis?
Case of Patient C

A. Mild cognitive impairment, amnestic
B. Mild cognitive impairment, nonamnestic
C. Alzheimer’s disease
D. Vascular dementia
E. Lewy body dementia
F. Parkinson’s dementia
Lewy Body Dementia

- Parkinsonian symptoms
- Gait abnormality
- Visual hallucinations (also delusions, auditory hallucinations, depression)
- Day-night reversal
- Memory problems precede motor symptoms
- 2 to 3-fold increased mortality with neuroleptics
- Extensive cholinergic neurotransmission

Parkinsons Dementia

- Affects up to 40% of Parkinsons patients
- Unclear if distinct from Lewy Body dementia
- Risk factors: Older age; onset of PD >60 yrs; long duration of PD; severe PD
- Visual hallucinations, paranoid delusions, depression, sleep disorders
**Parkinsons Dementia: Treatment**

- 15% response to rivastigmine in a 24-wk, double-blind, placebo-controlled trial (n=501)  
  *Cochrane database Syst Rev 2006*

- Smaller studies showing possible benefit from donepezil, galantamine

- Memantine showed improvement in clinical global improvement of change, but may increase hallucinations  
  *Lancet Neurol 2009;8:613*

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**Non-Pharmacologic Interventions for Dementia**

- Interventions for dementia may target three main functions of behavioral and psychological symptoms:
  - To obtain or meet a need (e.g. wandering)
  - To communicate a need (e.g. repetitive vocalizations)
  - To deal with an unmet need (e.g. aggression due to pain or discomfort)

- Caregiver training and support

- Setting goals-of-care and advance directives
What about Prevention?

Manage medical risk factors for CAD and CVA!
Dementia as a Spectrum

Prevention of Dementia

- Framingham Study
  - Lifetime risk of Alzheimer’s disease
    - 1 in 5 women
    - 1 in 10 men
  - 5-year delay in Alzheimer’s disease onset
    - Equivalent to lifetime risk reduction from 14% to 7%!

Seshadri S et al. Stroke 2006;37:344
Caregiver Stress

- 15 million caregivers provided 17 billion hours of care worth $203 billion (2010)
- Caregivers prone to depression, grief, fatigue, social relationship problems
- Caregiver stress related to premature institutionalization
- Screening of caregivers will identify those in need of more support

Source: Alzheimer’s Assoc

Caregiver Stress: Interventions

- Become familiar with resources
- Seek help from family, friends, caregivers
- Use relaxation techniques
- Get moving
- Make time for yourself
- Become educated about dementia
- Take care of yourself

Source: Alzheimer’s Assoc
Community Support & Services

- Adult day programs
- Support groups with respite
- Educational classes (dementia)
- IHSS or referral to community-based organization (CBO) for private caregiving ($$)
- Legal resources for DPAHC, placement planning, etc.
- In home care agencies
- Home safety programs

Multiple Chronic Conditions (MCC) & Dementia

- MCC
  - Duration of a year or more
  - Require ongoing medical attention and/or
  - Limitations in activities of daily living
- DM, CHF, CKD, Hyperlipidemia, Dementia
- Recognize that:
  - Dementia can make control of MCC more challenging
  - MCC can affect the risk and progression of dementia
Thank you for your attention!
dementia.uclahealth.org

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