Case

EM is a 79 year-old man with a h/o htn, DM2, CAD. His wife is concerned he is becoming “forgetful”. She notices that he frequently gets “lost”, is becoming more suspicious and “doesn’t make sense”. She wonders what can be done?

Questions...

- Does EM have dementia or Alzheimer’s Disease (AD)?
- How do I make the diagnosis?

Outline

- Clinical Presentation
- Diagnosis
- Updates in Treatment
- Challenging Behavioral Issues
- Updates in Prevention
- Resources
**Background**

- “We are who we are...because of what we have learned and what we remember” -- Nobel Laureate Dr. Eric R. Kandel
- AD prevalence 8% among people >65 years
  - Rates increase with age: 15-30% at age 85
- Costs $100 billion/yr

**Risk Factors for Alzheimer’s Disease**
- Age
- Down’s syndrome
- Head trauma
- Fewer years of formal education
- Female sex
- Family history

**Clinical Presentation**

- Cognitive changes
- Personality changes
- Changes in day-to-day functioning
- Psychiatric symptoms
- Problem behaviors
- Dementia under-diagnosed
  - High index of suspicion
  - Ask caregivers/surrounding family and friends

**Definitions of Dementia**

- Clinical (DSM4) diagnostic criteria
  - Memory impairment AND one or more:
    - Aphasia: language problems
    - Apraxia: motor problems
    - Agnosia: sensory problems
    - Disturbance in executive functioning
  - Deficits impair social/occupational function and represent a decline from baseline
Diagnosis of Dementia

- American Academy of Neurology recommendations:
  - Vitamin B12, thyroid, depression screen
  - Other tests as indicated: blood count, urine tests, liver tests, syphilis test, lumbar puncture
  - Head CT
- Do we need to do this?

“Reversible” Dementias...do they exist?

- Meta-analysis in 2003
  - 5620 subjects; potentially reversible causes in 9%; 0.6% actually resolved
- Causes of dementia in meta-analysis
  - 56% AD 20% vascular
  - 1% metabolic 0.9% depression
  - 0.1% medications
  - 15% Other (NPH, subdural hematoma, B12, tumor, Parkinson’s disease, HIV, frontal lobe)

- Most reversible dementias were in patients who:
  - Were relatively young
  - Had mild or atypical symptoms
- Neuroimaging detected conditions in 2.2%
  - 0.9% tumor, 1% NPH, 0.3% SDH
  - Most did not change course of illness
- Reversible dementias less common
- Must weigh costs/benefits of neuro-imaging

Diagnostic Instruments

- MMSE
  - Maximum score 30
  - Score <24 suggests delirium or dementia
    - Decline of 4 points over 1-4 years significant
  - Scores correlated with education level; inversely correlated with age
  - Not sensitive in people with higher levels of education
  - EM Score 16
Diagnostic Instruments

- **MMSE**
  - Survey of 18,056 adults
  - Scores relate to age
    - Median score 29 in those 18-24 years
    - Median score 25 in those >80 years
  - Scores relate to educational level
    - Median score 29 in those with >9 years schooling
    - Median score 22 in those with 0-4 years schooling

Crum RM et al. JAMA, 1993;269(18)

Diagnostic Instruments...Take Home Points

- **Caution in interpreting MMSE score**
  - Consider appropriate age/education median scores
  - MMSE scores for age/education:
    - www.nemc.org/psych/mmse.asp
  - Median LR for positive result 6.3 (CI 3.4-47)
- **Memory Impairment Screen better predictive value**
  - Recall 4 items from 4 categories
  - LR for positive result 33!


Diagnostic Instruments...Take Home Points

- **Highly educated individuals**
  - Hopkins Verbal Learning Test
    - Given 12 words; check recall on 3 different trials
    - Decoy words given
  - Neuropsychological testing
    - May be better in detecting early impairment in highly educated individuals


Diagnosis of Dementia

- **Tests not ready for “prime time”…**
  - PET scanning
  - CSF β-amyloid
  - CSF tau
  - APOEε4 genotyping
- **Not enough evidence for USPSTF to recommend screening for dementia in primary care**
Pathophysiology of Alzheimer’s Disease

- **Neuritic plaques**
  - Beta amyloid protein
  - Accumulation initiates cell death
- **Neurofibrillary tangles**
  - Filaments of abnormally phosphorylated tau protein
- **Loss of neurons**
  - Cholinergic, noradrenergic, serotonergic neurotransmitters

Case

- 78 year-old woman recently diagnosed with Alzheimer’s Disease. MMSE score is 19. Her family is interested in doing “anything” to treat this disease. What treatment can you offer her?

Treatment of AD

- **Clarify goals**
  - Preserve function and independence
  - Maintain quality of life
  - Minimize excess disability and ensure safety
  - Make long-term decisions early
- **Treatment Options**
  - Symptomatic treatment of memory disturbance
  - Symptomatic treatment of behavioral disturbance
  - Disease-modifying treatment

Symptomatic Treatment of Memory Disturbance

- Cholinesterase Inhibitors delay degradation of acetylcholine at the synaptic cleft. Indicated for mild-moderate Alzheimer’s Disease
  - Tacrine (Cognex)
    - Not used due to liver toxicity
  - Donepezil (Aricept)—5-10mg/day
  - Rivastigmine (Exelon)—6-12mg/day
    - May cause weight loss
  - Galantamine (Razadyne)—24-32mg/day or patch 4.6-9.5mg
    - May cause weight loss
Cholinesterase Inhibitors

- Donepezil and Galantamine
  - Metabolized by cytochrome P450 system
- ChEIs
  - Common side effects: nausea, vomiting, diarrhea
    - Take with food
    - Interruption of meds = start back at lowest dose
    - If changing meds due to SE, washout period 7-14 days

Cholinesterase Inhibitors...What’s the Data?

- Studies range 12 weeks to 3 years
  - Pts on ChEIs compared to placebo
    - Outcome ADAS-cog
      - ADAS-cog evaluates memory, attention, language, orientation (score 0-70)
      - Average difference on ADAS-cog -4
    - Outcome Clinician Interview Based Assessment of Change
      - Statistically significant differences, but most do not show clinically significant changes
      - More evidence with galantamine and rivastigmine


What’s Clinically Significant?

- Long-term donepezil treatment evaluated
  - 565 patients with mild-mod AD randomly assigned to donepezil 5mg or placebo for 12-week run-in
  - 486 patients second randomization to 5mg, 10mg, or placebo for 48 weeks, followed by washout period and then further treatment (up to 3 additional years)
  - End points: Institutionalization or progression of disability (loss of ADLs)


What’s New in Symptomatic Memory Treatment?

- Long-term donepezil treatment
  - No difference in primary outcomes
    - Institutionalization at 3 years 42% donepezil vs. 44% placebo
    - Disability progression 58% vs. 59%
  - No difference in care costs, unpaid caregiver time, behavioral/psychological symptoms
  - Costs of drug not offset by any positive outcomes

Cholinesterase Inhibitors...Take Home Points

- Likely no disease modifying effects
  - Delay progression 6mo-1yr
- Modest cognitive improvement
  - Guidelines: “Base the decision to initiate therapy on individualized assessment”
- Insufficient evidence regarding head-to-head comparisons; choose medication based on SE and dosing

Case

- 80 year-old woman with progression of her Alzheimer’s Disease. She is currently being treated with Aricept at 10mg/day. Her recent MMSE=11. Are there other treatment options?

Other Options in Memory Treatment?

- Memantine (Namenda)
  - NMDA-receptor antagonist
    - Glutamate stimulates NMDA receptor; overstimulation results in neuronal damage
  - Dosing 10-20mg/day
  - Studied in moderate-severe AD
    - Pooled estimate from 3 trials (vs. placebo)
      - Statistically significant improvements on ADAS-cog scale but not clinically important

Other Options in Memory Treatment?

- Memantine combined with donepezil
  - 404 patients with mod-severe AD on donepezil randomized to memantine or placebo
  - Outcomes: cognition (40-item Severe impairment battery) and AD Cooperative Study-ADLs
  - Results: scores favored memantine
    - SIB improved 0.9 (memantine) vs. –2.5 (placebo)
    - ADCS-ADL –2.0 vs. –3.4

Tariot PN et al. JAMA, 2004;291(3).
Guidelines in Memory Treatment?

- **Take Home Points…**
  - First line therapy in mild-mod AD (if treatment decided) is cholinesterase inhibitors
    - If treatment failure/not tolerated, can either:
      - Change to another ChEI
      - Add memantine
      - Change to memantine
      - Long-term donepezil may not be cost-effective but hard to estimate individual benefits
    - Consider memantine for moderate-to-severe dementia

- **When to stop treatment?**
  - If quality of life benefits no longer possible (as determined by family, provider)
  - Pt dependent in all basic activities of daily living

Disease-Modifying Treatment of AD

- **Anti-inflammatories?**
- **Anti-oxidants?**
  - Vitamin E
  - Selegeline
- **Ginkgo biloba?**

Treatment of AD with Anti-Inflammatory Drugs

- AD brain with acute phase reactants and immune-related markers
- NSAIDS to treat AD
  - Negative trial of prednisone vs. placebo
  - Negative trials of diclofenac/misoprostol
  - Negative trial of rofecoxib or naproxen vs. placebo

Aisen PS, et al. JAMA, 2005;293.
Treatment of AD

Vitamin E and Selegiline

- Free radicals and oxidative damage contributes to neuronal death
  - Vitamin E traps free radicals; selegiline acts as anti-oxidant
- Alzheimer’s Disease Cooperative Study
  - 341 moderate AD patients; followed 2 yrs
  - Vitamin E 1000U BID, selegiline 5mg BID, both, placebo
  - Endpoints: nursing home placement, progression to severe dementia, loss of ADLs, death

Sano et al.  NEJM, 1997;336

Treatment of AD

Vitamin E and Selegiline

- Time to primary endpoints:
  - Vitamin E: 670 days (P=.001)
  - Selegiline: 655 days (P=.012)
  - Both: 585 days (P=.049)
  - Placebo: 440 days

Side Effects of Vitamin E?

- Can increase risk of bleeding—particularly in pts on coumadin
- Meta-analysis of 19 RCT
  - 135,967 patients on vitamin E (16.5-2000 IU/d)
  - Dose >400 IU associated with increased mortality (Risk difference 39 per 10,000 people CI 3-74)
  - Lower-dose vitamin E associated with decreased mortality
- IOM now recommending dose <1100 IU/day


Treatment of AD

Ginkgo Biloba

- Cochrane review of Ginkgo
  - Most studies small, poor methodology
  - Evidence of clinically significant benefit is inconsistent
  - Appears to be safe in side effect profile
- Currently, not recommended
- Problem: lack of regulation with ginkgo

**Disease-Modifying Treatments...Take Home Points**

- Vitamin E is recommended…for now
  - Guidelines 1000 IU BID; IOM 1000 IU daily
- Insufficient evidence for anti-inflammatories
- Insufficient evidence for ginkgo

**Behavioral Issues...**

- Don’t forget environment manipulation
- Low threshold for treatment of depression
- SSRIs first-line for depression treatment
- Atypical antipsychotics for treatment of psychosis and agitation

**Prevention of AD Case**

60 year-old woman with strong family history of Alzheimer’s Disease. She is concerned about her own risk for dementia. What is the best prevention treatment can you offer?

A) Control her BP  
B) She should start ERT  
C) She should take a statin  
D) She should start an NSAID

**Prevention of AD**

A role for controlling BP?

- SYST-EUR study
  - >3000 patients over 60 with htn
  - BP protocol meds vs. placebo
  - Outcome: dementia (MMSE, diagnostic testing)
  - Incidence of dementia 7.7 cases per 1000 (placebo) compared to 3.8 (treatment)
- Meta-analysis of 4 RCT trials: RR dementia after htn rx=0.80 (0.63-1.02)

Updates in Prevention
Estrogen/Progestin

• Women’s Health Initiative Memory Study
  – 4532 healthy post-menopausal women (65-79)
  – Randomized to estrogen/progestin or placebo
  – Outcome “probable dementia”
    • 40 cases in ERT group
    • 21 cases in placebo group
    • Estrogen/progestin increased risk for probable dementia (HR 2.05)

Updates in Prevention
Estrogen Only

• Women’s Health Initiative Memory Study
  – 2947 healthy post-menopausal women
  – Randomized to estrogen only or placebo
  – Outcome “probable dementia” and mild cognitive impairment
    • Increased risk of development of probable dementia (HR 1.49)
    • Pooled data increased risk (HR 1.76; CI 1.19-2.6)

More on Estrogen/Progesterone

• Cohort study from Olmsted County, MN
  – All women 1950-1987 who underwent oophorectomy prior to menopause for non-cancer indication
    • 1,433 with unilateral; 1,824 with bilateral
  – Each cohort member matched to control
  – Median f/u 29.2 years
  – Oophorectomy before menopause: Increased risk of dementia compared to control (HR 1.46, CI 1.13-1.9)

Updates in AD Prevention
Should Statins be in the Water?

• RCT: Pravastatin vs. placebo in 5804 people aged 70-82 years
  – No difference in cognitive function after 3.2 years
• RCT: Simvastatin vs. placebo in 20,536 people aged 40-80
  – No difference in incidence of dementia
**Prevention of AD with Anti-Inflammatory Drugs**

- Meta-analysis of observational studies
  - NSAIDS >2yrs reduced risk by 73%
  - Confounding?
- Recent RCT
  - 2528 volunteers >70 yrs with FH AD
    - Naproxen vs. Celebrex vs. Placebo
  - Study stopped after 3 years: no evidence anti-inflammatories prevent AD

BMJ, 2003;327, Neurology 2007;68

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**Antioxidants and AD Prevention**

- Prospective cohort study of 5395 patients
  - High intake antioxidants associated with lower risk for AD
    - Vitamin C reduction of 18%
    - Vitamin E not statistically significant reduction
- Prospective Study of 815 patients
  - Vitamin E protective only if APOE ε4 negative
- Prospective cohort study of 980 patients
  - No benefit of anti-oxidants

JAMA, 2002;287(24), JAMA, 2002;287(24), Arch Neu, 2003;60

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**Leisure Activities and Risk of AD**

- 775 older adults followed for 5 years
  - Current and past cognitive activities rated
  - Higher rate of participation in cognitive activity was associated with reduced incidence of AD (HR 0.58)


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**Prevention of AD Case**

60 year-old woman with strong family history of Alzheimer’s Disease. She is concerned about her own risk for dementia. What is the best prevention treatment can you offer?

A) Control her BP
B) She should start ERT
C) She should take a statin
D) She should start an NSAID
**Exercise and Dementia Prevention**

- Honolulu-Asia Aging Study
  - 2257 men ages 71-93 years
  - Men who walked the least (<.25 mile/d) had 1.8 fold excess risk of dementia compared to those who walked >2 miles/d
    - Adjusted for baseline cognitive function; still significant


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**Exercise and Dementia Prevention**

- Nurses Health Study
  - 18,766 women
  - 20% lower risk of cognitive impairment in those with the highest level of activity
  - Even walking 1.5 miles/week associated with better cognitive performance
  - Confounders?


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**Obesity and Risk of AD**

- Kaiser Permanente 6,583 members
  - Sagittal abdominal diameter (SAD) measured 1964-1973 with medical records f/u 1994-2006
  - Higher SAD associated with increased dementia risk
    - Highest quintile of SAD: HR for dementia 2.72 (CI 2.33-3.33)
    - Highest quintile of SAD adjusted for BMI: HR 1.98 (1.33-2.32)
  - Thigh adiposity didn’t increase dementia risk


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**Prevention of AD...Take Home Points**

- Lots of reasons to control BP
- Estrogen replacement therapy is out for now…
- Need more evidence regarding statins…
- Jury still out on NSAIDS
- Likely no effect from anti-oxidants
- Chess never hurt anyone
- Be a “pear” rather than an “apple”
- Get out there and exercise!
Treatment of Caregivers!

- Randomized study of 120 caregivers
  - Treatment group: counseling, support groups
  - Outcome: time to nursing home placement
  - Result: “treatment group” median time to placement was 329 days longer

Treatment of Caregivers!

- Assessment of 217 caregivers
  - Half reported helping with ADLs >46 hrs/week
  - 59% felt they were “on duty” 24 hrs/day
  - High levels of depression while providing care
    - Depression markedly improved one year after death of patient
    - 72% “relieved” at the death of their loved one

Resources

- Alzheimer’s Disease Education and Referral (ADEAR) Center 800-438-4380
  - www.alzheimers.org
- Alzheimer’s Association 800-660-1993
  - www.alz.org and www.alzsf.org
  - Safe Return Program
- American Academy of Neurology
  - www.aan.com/professionals/practice/guidelines.cfm