Update in the Diagnosis, Treatment and Prevention of Alzheimer’s Disease

Katherine Julian, M.D.
Associate Clinical Professor of Medicine
University of California, San Francisco
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Conflicts of Interest

- No Conflicts of Interest
Case

EM is a 67 year-old man with a h/o high blood pressure. Brought in by wife who is reporting that patient’s personality has changed over the last year. He is becoming more suspicious, and at times talks and “doesn’t make sense”.

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

AD Prevalence

- AD estimated prevalence 24.3 million world-wide in 2001
- Predicted rise to 42.3 million in 2020
- 81.1 million by 2040
- Lifetime risk of dementia after age 65 is 17-20%
- Costs $150 billion/yr

Dementia Types

- Alzheimer’s: most common, 70%
- Vascular dementia: approx 17%
- Other types: 13%
  - Parkinson-related
  - Alcohol
  - Dementia with Lewy Bodies

Pathophysiology of AD

- Neuritic plaques
  - Amyloid precursor protein cleaved
  - Makes beta amyloid protein
  - Accumulation initiates cell death
- Neurofibrillary tangles
  - Filaments of abnormally phosphorylated tau protein
- Loss of neurons
  - Cholinergic, noradrenergic, serotonergic neurotransmitters
- Is it amyloid deposition that kills neurons OR are neurons being damaged by something else?
Risk Factors for AD/Dementia

- Age
- Down’s syndrome
- Head trauma
- Fewer years of formal education
- Female sex
- Family history
- Vascular risk factors (DM, htn, smoking)

Clinical Presentation of Dementia

- Cognitive changes
- Personality changes
- Changes in day-to-day functioning
  - IADLs that require calculation/planning first to be impaired
- Psychiatric symptoms
- Problem Behaviors
- Dementia under-diagnosed
  - High index of suspicion
  - Ask caregivers/surrounding family and friends
Rapid Screening for Cognitive Impairment

- Routine screening not recommended; complete screen for those who screen positive
- Verbal Fluency Test: best screening test
  - Sensitivity 88%; specificity 96%
  - One minute
  - Ask patient to name as many animals as possible in one minute
  - 1 point/animal
  - Score <15 suggestive of dementia
    - Score <12 if 1-7 years of school
    - Score <9 if no education

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, represent a decline from baseline, not from delirium
- Mild cognitive impairment: impairment doesn’t affect function
  - Amnestic vs. nonamnestic
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
  - Neuro imaging (CT or MRI)
- 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)

Clarefield AM. Archives of Internal Medicine, 2003;163.
“Reversible” Dementias…do they exist?

- 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
  - AGS recommends imaging: age <60, rapid decline (weeks/months), CA, HIV, anti-coagulation

Clarfield AM. Archives of Internal Medicine, 2003;163.

Neuro-Imaging – Updates

- Semi-quantitative MRI
  - Medial temporal lobe atrophy in AD
  - New studies looking at hippocampal and cortical thickness measurement
- PET with fluorodeoxyglucose measures glucose metabolism (18F-FDG-PET)
  - Hypometabolism in temporal/parietal regions
  - Approved in US for dx purposes of AD in early stages
  - Sens/spec estimate 86% (wide variation)
  - PET with beta-amyloid ligands will visualize beta-amyloid deposition
- May overlap with other brain pathologies
Example of $^{18}$F-FDG-PET

Diagnosis of AD – Updates

- Abnormal CSF biomarkers
  - Low beta-amyloid
  - Increased tau/phosphotau concentrations
  - No consensus on cutoff points for real practice
- Perfusion SPECT
  - Resolution less but less expensive
Diagnostic Instruments

- Mini Mental Status Exam
  - 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

- Montreal Cognitive Assessment

**EM Score 17**

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:
  - Median LR for positive result 6.3 (CI 3.4-47)
- If positive initial screen (verbal fluency), do follow-up test (MMSE, MOCA)


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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

Diagnostic Instruments…Take Home Points

- Tests not quite ready for “prime time”…
  - PET scanning (although approved)
  - MRI
  - CSF β-amyloid
  - CSF tau
  - APOEε4 genotyping
- Not enough evidence for USPSTF to recommend screening for dementia in primary care

Case

78 year-old woman recently diagnosed with Alzheimer’s Disease. MMSE score is 19. What should you do next?

1) Start an acetylcholinesterase inhibitor (ex: donepezil or aricept)
2) Do not start any medications at this time
3) Discuss with the family/patient their wishes regarding treatment
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
  - 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
  - Vivid dreams: take in am
  - Bradycardia, AV block

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
  - Followed up to 3 years
  - End points: Institutionalization or progression of disability (loss of ADLs)


Symptomatic Memory Treatment?

- Long-term donepezil treatment
  - No difference in rates of institutionalization or disability progression
  - 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

78 year-old woman recently diagnosed with Alzheimer’s Disease. MMSE score is 19. What should you do next?

1) Start an acetylcholinesterase inhibitor (ex: donepezil or aricept)
2) Do not start any medications at this time
3) Discuss with the family/patient their wishes regarding treatment
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
  - 24-week study
  - Outcomes favor memantine but once again, not clinically significant

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
Guidelines in Memory Treatment?

- 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
- No evidence for NSAIDS to treat AD
  - Prednisone vs. placebo
  - Diclofenac/misoprostol
  - Rofecoxib or naproxen vs. placebo

ADAPT Research Group, Arch Neurol, 2008

Treatment of AD Vitamin E and Selegiline

- Free radicals and oxidative damage contributes to neuronal death
  - Vitamin E traps free radicals; selegiline acts as antioxidant
- Older study showing some benefit of vitamin E
- Updated Cochrane review: no benefit of vitamin E

Sano et al. NEJM, 1997;336
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 <1000 IU/day


Treatment of AD
Ginkgo Biloba

- Cochrane review of Ginkgo
  - Most studies small, poor methodology
  - Evidence=inconsistent benefit
  - High doses: GI SE, may increase bleeding in patients on ASA/coumadin
- 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
  - Low-dose even better!
- Insufficient evidence for anti-inflammatories
- Insufficient evidence for ginkgo

New Directions for AD Treatment...

- Clearance of beta-amyloid through immunotherapy?
- Inhibit the enzymes that cleave amyloid pre-cursor protein?
- Anti-tau agents?
- Lower beta-amyloid levels?
  - Prelim evidence from RCT, double-blind placebo-controlled trial in 1684 patients with mild AD
    - No difference in outcomes
    - Other agents being studied

Green RC, et al. JAMA, 2009;302(23)
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) She should start ERT
B) She should take a statin…forget about that package warning!
C) She should start an NSAID
D) She should exercise

Updates in Prevention
Estrogen Replacement Therapy

- Women’s Health Initiative Memory Study
  - 4532 healthy post-menopausal women (65-79)
    - Randomized to estrogen/progestin or placebo
    - Estrogen/progestin increased risk for probable dementia (HR 2.05)
  - 2947 randomized to estrogen only or placebo
    - Increased risk of development of probable dementia (HR 1.49; CI 0.83-2.66)
    - 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)


Estrogen/Progesterone

- Is there a “window of opportunity” when hormones are actually beneficial?
**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
- **No evidence statins prevent vascular dementia**

Heart Protection Study Collaborative Group. Lancet, 2002;360.

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**NYT Article...**

**“Do Statins Make You Stupid?”**

- Reports that statins may worsen cognition
  - Only seen in a few case reports (described in 60 adults)
- Review of all statin studies: benefits outweigh risks
  - 1 RCT simvastatin impaired some measures of cognition compared to placebo
  - Majority of trials: statins with either a neutral or beneficial effect on cognition
  - Preliminary data: hydrophilic statins (i.e., pravastatin and rosuvastatin) may be less likely to contribute to cognitive impairment due to limited penetration across the blood-brain barrier

Prevention of AD with Anti-Inflammatory Drugs

- Meta-analysis of observational studies
  - NSAIDS >2yrs reduced risk by 73%
  - Confounding?
- 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)

Sleep-Disordered Breathing

- 298 older women without dementia followed prospectively
- 1 sleep study overnight
  - Sleep-disordered breathing=15 (or more) apnea-hypopnea events per hour of sleep
- Followed average 4.7 years
- Women with sleep-disordered breathing more likely to develop MCI or dementia (44.8% vs. 31.1% in controls)
- Adjusted for age, race, BMI, education level, baseline cognitive scores, sedating meds, DM/htn

Yaffe K, et al. JAMA, 2011
Obesity and Risk of AD

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


Exercise and Dementia Prevention

- RCT of a 24 week exercise program in 138 participants who reported memory problems but didn’t meet dementia criteria
  - Home-based program of physical activity
  - Modest improvement in cognition over an 18-month follow-up period
- 13 studies with over 150,000 participants – meta analysis
  - Dementia RR 0.72 (CI 0.6-0.96)
  - AD RR 0.55 (CI 0.36-0.84)

Lautenschlager NT et al. JAMA, 2008
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)

Prevention of AD – Cognitive Reserve

- Evidence suggests that cognitive reserve is protective against AD
  - Education
  - Occupation
  - Mental activities
β-Amyloid 42/40, Cognitive Reserve and Cognitive Decline

Prevention of AD…Take Home Points

- Estrogen replacement therapy is out for now…
- Need more evidence regarding statins…
- Jury still out on NSAIDS
- Get out there and exercise!
- Be a “pear” rather than an “apple”
- Chess never hurt anyone
- Stay in school
Prevention of AD
Case

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Prevention of AD – Stay Positive!

- Observational studies with increased dementia risk
  - Mid-life htn
  - Current Smoking
  - Diabetes
- No evidence yet that treatment decreases dementia risk
Prevention of AD – Stay Positive!

• To estimate impact of risk factor reduction on AD prevalence for 7 modifiable factors:
  ▪ Diabetes
  ▪ Mid-life hypertension
  ▪ Mid-life obesity
  ▪ Depression
  ▪ Physical inactivity
  ▪ Low education
  ▪ Smoking

• Population attributable risks (PARs)
  • Tools to estimate proportion of disease attributable to given risk factor, accounting for prevalence & strength of association

• Calculations
  • Risk factor prevalence worldwide, U.S.
  • Relative risk from most recent/comprehensive meta-analysis or systematic review

Barnes, DE and Yaffe K. Lancet Neurol, 2011;10
Evaluation of Driving Risk in Dementia – Practice Parameter

- Patient is at increased risk for unsafe driving if:
  - Clinical Dementia Rating Scale $\geq 0.5$ (level A)
  - Caregiver rates patient’s driving ability as marginal or unsafe (level B)
  - Pt has a h/o crashes/traffic citations (level C)
  - Pt has reduced driving mileage or self-reported situational avoidance (level C)
  - MMSE $\leq 24$ (level C)
  - Pt with aggressive/impulsive personality characteristics (level C)


Resources

- Alzheimer’s Disease Education and Referral (ADEAR) Center 800-438-4380
  - http://www.nia.nih.gov/alzheimers
- Alzheimer’s Association 800-272-3900
  - www.alz.org
  - Safe Return Program
- American Academy of Neurology