Update in the Diagnosis, Treatment and Prevention of Dementia*

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Conflicts of Interest

- No Conflicts of Interest
Case

EM is a 67 year-old woman with a h/o high blood pressure. Brought in by husband who is reporting that patient’s personality has changed over the last year. She 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
- 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: 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
Definitions of Dementia* by DSM5

Dementia
- No longer using the term “dementia”
- Neurocognitive disorder
  - Due to...
    - Alzheimer’s Disease
    - Vascular Disease
    - Lewy Body, etc

DSM5 Neurocognitive Disorders (NCD)

- Minor neurocognitive disorder
  - Modest cognitive decline from a previous baseline
  - Can be in any domain (ex: memory, language, executive function, etc)
  - Based on pt’s concerns AND knowledgeable informant (or clinician) AND
  - Decline in neurocognitive performance (1-2 SD below normal) on formal testing or equivalent clinical evaluation
  - Cognitive decline doesn’t interfere with independence but requires some compensation
  - Can’t occur due to delirium
  - Deficits can’t be from another mental disorder (ex: depression)
- Example: Mild cognitive impairment: impairment doesn’t affect function
DSM5 Neurocognitive Disorders (NCD)

- **Major neurocognitive disorder**
  - Evidence of substantial cognitive decline in one or more domains
  - Based on pt’s concerns AND knowledgeable informant (or clinician) AND
  - Decline in neurocognitive performance (≥2 SD below normal) on formal testing or equivalent clinical evaluation
  - Cognitive decline is sufficient to interfere with independence (ex: requires assistance with IADLs or ADLs)
  - Can’t occur due to delirium
  - Deficits can’t be from another mental disorder

Rapid Screening for Cognitive Impairment

- 3/14 USPSTF insufficient evidence to recommend for or against screening (for dementia and MCI)
- Variety of office screening tests
  - MMSE most studied: sens 88.3%; spec 86.2%
  - (MOCA sens 90% in limited studies for MCI)
  - Clock drawing sens range 67-97%; spec 69-94.2%

2014 USPSTF Consensus Statement
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

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)
Work-Up of Cognitive Impairment

- 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)

Clarfield 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.

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Neuro-Imaging – Updates

- Semi-quantitative MRI
  - Medial temporal lobe atrophy in AD
  - New studies looking at hippocampal and cortical thickness
- Aβ PET with florbetapir F-18 (Amyvid) highlights brain beta-amyloid
  - Approved by FDA April 2012
  - Median sensitivity 92% (range 69-92%) and median specificity 95% (range 90-100%)
  - Positive scan does not establish the dx—use as adjunct
- May overlap with other brain pathologies

Example of $^{18}$F-FDG-PET

Normal Aging vs. Alzheimer’s Disease
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

- Caution in interpreting MMSE score
  - Consider appropriate age/education median scores
  - MMSE scores for age/education available on the web
  - Median LR for positive result 6.3 (CI 3.4-47)
- If positive initial screen, can consider further testing if appropriate


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Diagnostic Instruments

- Highly educated individuals
  - Neuropsychological testing
    - May be better in detecting early impairment

Diagnostic Instruments…Take Home Points

- Tests not quite ready for “prime time” but coming…
  - PET scanning (although approved)
  - MRI (atrophy of temporal lobe)
  - 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) Start memantine
3) Do not start any medications at this time
4) 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
    - 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

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 – modest cognitive improvement
  - Delay progression 6mo-1yr
  - Guidelines: “Base the decision to initiate therapy on individualized assessment”

- Insufficient evidence regarding head-to-head comparisons; choose medication based on SE and dosing

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1) Start an acetylcholinesterase inhibitor (ex: donepezil or aricept)
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Other Options in Memory Treatment?

- 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 Mod-Severe AD?

- Memantine (Namenda)
  - NMDA-receptor antagonist
    - Glutamate stimulates NMDA receptor; overstimulation results in neuronal damage
    - Pooled estimate from 3 trials (vs. placebo)
      - Statistically significant improvements on ADAS-cog scale but modest clinical improvement
  - Memantine combined with donepezil

Tariot PN et al. JAMA, 2004;291(3).
Other Options in Mod-Severe AD?

- New dose of donepezil 23mg daily approved 2010 for moderate-severe AD

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 (or increase donepezil)
  - 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-oxidants?
  - Vitamin E
- Anti-inflammatory?
- Statins?
- Ginkgo biloba?
Treatment of AD: Vitamin E

- Free radicals and oxidative damage contributes to neuronal death
  - Vitamin E traps free radicals
- Mixed results in studies
  - 1997 study showing some benefit of vitamin E
  - 2008 Cochrane review: no benefit of vitamin E
  - 2014 JAMA: 2000 IU resulted in slower decline (approx. 6 mo) in mod-sev AD. Study underpowered

Sano et al. NEJM, 1997;336
Dysken MW, JAMA, 2014;311(1)

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 recommending dose <1000 IU/day

Treatment of AD

- Negative trials
  - Anti-inflammatories (ibuprofen, naproxen, celecoxib, indomethacin)
  - Statins (simvastatin, atorvastatin)
  - Dietary supplements (multi-vitamins, fatty acids)
    - Mixed data on Gingko – Cochrane review inconsistent benefit
    - High doses: GI SE, may increase bleeding in patients ASA/coumadin


Disease-Modifying Treatments...Take Home Points

- Mixed evidence for Vitamin E
  - (Old) guidelines 1000 IU BID; IOM 1000 IU daily
  - No evidence for other treatments
What’s Next?

Amyloid precursor protein (APP) $\rightarrow$ amyloid-beta fragments

\[ \beta\text{-secretase} \quad \text{Y-secretase} \]

- Inhibitor of Y-secretase: Semagacestat
- Monoclonal Ab binds soluble amyloid beta fragments
  - Solanezumab
  - Bapineuzumab

What’s Next?

- Question: Does semagacestat improve cognition in patients with probable Alzheimer’s disease?
- Study Design: Double-blind, PCT 1537 patients semagacestat (2 doses) vs. placebo
- Outcomes: Terminated early—worsened cognition scores, more weight loss, skin cancers, infections

What’s Next?

- Question: Do monoclonal antibodies Solanezumab and Bapineuzumab improve cognitive scores in mild-mod AD
- Study Design: 2 double-blind, RCT
- Outcomes: No improvement in cognitive testing. Safety finding: more brain edema


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)


More on Estrogen/Progesterone

- Olmstead county cohort: 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
  - Oophorectomy before menopause: Increased risk of dementia compared to control (HR 1.46, CI 1.13-1.9)

Estrogen/Progesterone

- Findings supported by 2 other cohort studies showing earlier age with surgical menopause associated with cognitive decline

- 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.
Reports that statins may worsen cognition
- 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
- 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 and AD

- Sleep and AD = bidirectional relationship
  - Brain regions involved in sleep and circadian control affected early in AD
  - Patients with AD often have worse quality of sleep
  - Sleep changes may precede onset of cognitive symptoms
    - Amyloid deposition associated with worse sleep quality
- Chicken or the egg?
- Chronic disrupted sleep likely has some cognitive effect

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

- Meta-analysis
- 33,816 non-demented patients followed prospectively
- Subjects with high-level physical activity protected against cognitive decline (HR 0.62 CI 0.54-0.7)
- Low-moderate exercise also protective (HR 0.65; CI 0.57-0.75)


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

Yaffe K, et al. JAMA, 2011;305(3)
Prevention of AD…Take Home Points

- Estrogen replacement therapy is out for now…
- Statins good for hyperlipidemia but not to prevent dementia
- 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

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

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
**Prevention of AD – Stay Positive**

![Chart showing the number of AD cases prevented worldwide with 10% and 25% reductions for various factors like low education, smoking, physical inactivity, depression, mid-life obesity, diabetes, and combined.](chart)

Barnes DE and Yaffe K. Lancet Neurol, 2011

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**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