Early Diagnosis of Dementia
Does it really matter?

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Disclosure Statement of Financial Interest
I, Monica Crane, MD……

DO have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

My presentation has been peer reviewed by ETSU, and has been found to be balanced, evidence based, and free of commercial bias.

Potential Conflict of Interest Disclosure

Those Relationships Are With:

Eisai/Pfizer Pharmaceuticals
Forest Pharmaceuticals
Novartis Pharmaceuticals
### Objectives

- Normal Aging
- Protective factors and risk factors
  - Early diagnosis of Alzheimer’s Disease
  - Clinical criteria
  - Why does it matter?
  - Dementia subtypes
  - Treatment

### Normal Aging

- Intelligence: stable or ↑
- Attention: stable or mild ↓
- Language: stable
- Memory: mild ↓
- Visuospatial: mild ↓
- Executive function: mild ↓ (reasoning, cognitive flexibility, problem solving)
- Speed: always ↓
  - Slowing of thought and action is the most reliable aging change!

### AD risk factors

<table>
<thead>
<tr>
<th>Fixed Risk Factors</th>
<th>Modifiable Risk Factors</th>
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<tbody>
<tr>
<td>Age</td>
<td>Lack of exercise</td>
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<tr>
<td>Family history</td>
<td>Smoking</td>
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<tr>
<td>Genetics</td>
<td>High blood pressure and heart disease</td>
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<tr>
<td>Mild Cognitive Impairment (MCI)</td>
<td>High cholesterol</td>
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<td>Poorly controlled diabetes</td>
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<td>Low education</td>
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What were the old Alzheimer’s disease research criteria?

- Old criteria: DSM-IV NINCDS-ADRA criteria validated against neuropathological gold standards
- **VERY POOR** specificity (23-88%)
- Old definitions had good detection of a dementia syndrome (65-96%) but it was often NOT AD
- **There are over 20 common dementia subtypes and 50+ other rare dementia subtypes**

Auguste Deter, first diagnosed AD patient, 1906.


Newly Proposed Criteria for probable AD

- **Significant abnormality in episodic memory for ≥ 6 months & at least ONE objective biomarker:**
  - Medial temporal and medial/posterior parietal lobe atrophy
  - Abnormal CSF* (95% sensitive, only 29% specific)
    - Low amyloid B1-42 concentrations
    - Increased total tau and phospho-tau
  - FDG-PET scan: AD pattern
  - Florbetapir F18 (Amyvid)-PET scan: positive
  - Genetics (PSEN1, PSEN2, APP, trisomy 21)


Medial temporal lobe atrophy

Normal Alzheimer’s

T1 MRI coronal view
Limbic System: **Hippocampus**

- Stores new memories or “working memory”
- NEW finding: important in our ability to envision the future and replay events that were never experienced
- Important in planning and imagination


**Q:** What is happening to the brain in Alzheimer’s disease?

**A:** You would see hallmark neuropathologic lesions: plaques, tangles with brain atrophy and loss of neurons and synapses.

Florbetapir (Amyvid) binds to amyloid aggregates (β-amyloid neuritic plaque) in the brain

- $^18$F-florbetapir-PET scan

(Neurology doi: 10.1212/WNL.0b013e3182661f74.)
Why diagnosis early?

1. Early diagnosis allows prompt treatment of reversible symptoms (such as other comorbid illnesses exacerbating the impairment).
2. Alzheimer’s is not curable but is treatable.
3. Early diagnosis gives a patient and their family more time to arm themselves with knowledge about the disease and the best way to live with the disease. Knowledge is empowering.
4. Early diagnosis and treatment can prevent hospitalization and save health care dollars!

Why should I tell you and your family about the diagnosis?

1. Early diagnosis will help you and your family understand why you are having symptoms.
2. Early diagnosis gives you more time to make big life decisions: financial planning, power of attorney, living wills.
3. Early diagnosis maximizes your safety and safety of your family.

Early diagnosis allows treatments for AD that help slow its progression.

The big challenge for clinicians... there are many dementia types other than AD
### Dementia Prevalence

(% of each type seen in US)

- **Alzheimer’s Disease ~ 50-80%**
- **Vascular dementia ~ 5-10%**
- **Dementia with Lewy Bodies & Parkinson’s disease dementia ~10%**
- **Frontotemporal Dementias ~10%**

### Heterogeneity of dementia

- **Alzheimer’s Disease**
  - Posterior cortical atrophy
  - Progressive aphasia
  - Amnestic variant
- **Vascular dementia**
  - Large vessel (stroke)
  - Small vessel disease/ subcortical
  - CADASIL, CAA
- **Parkinson’s disease dementia and related disorders**
  - Parkinson’s disease dementia and Lewy Body Dementia
  - Multiple System Atrophy
- **Frontotemporal Dementia disorders**
  - Behavioral variant FTD
  - Corticobasal degeneration and Progressive supranuclear palsy
  - Primary Progressive Aphasia and Semantic dementia
- **Motor neuron diseases**

### Vascular Dementia
Vascular dementia

- Large vessel disease (post-stroke)
- Small vessel disease
  - Executive function problems
  - Gait disorder
  - Depressive symptoms
  - Emotional lability
  - Memory problems

Cerebrovascular disease and “vascular depression”

Striato-pallido-thalamo cortical pathways disrupted by vascular lesions.


Lewy Body Dementia

Degeneration of an area in the brain stem called the substantia nigra similar to Parkinson’s disease

Degeneration of cortical areas of the brain similar to AD
**Dementia with Lewy Bodies (DLB) versus dementia in Parkinson's disease (PDD)**

- LBD is an umbrella term for two related clinical diagnoses: DLB and PDD.
- Patients with dementia before or within 1 year of Parkinson's symptoms are diagnosed with DLB.
- People who have an existing diagnosis of Parkinson's for ≥ 1 year diagnosed w PDD.

**Clinical Features of Lewy Body Dementia**

- Fluctuating cognition
- Memory loss
- Hallucinations
- Symptoms that resemble Parkinson's disease
- Gait changes
- Autonomic dysfunction
- Depression
- Poor reaction to dopamine agonists and/or antipsychotic drugs (Positive response to cholinesterase inhibitors, memantine)

**Frontotemporal dementias**
"Dementia That's Neither Alzheimer's Nor Easy"

FDG-PET images of metabolic activity: healthy controls, AD, and FTD. Scale red (high FDG uptake)-yellow-green-blue (low FDG uptake).

Photo Credit: Dr. Janet Miller, Dr. Susanna Lee, MGH Harvard, Radiology Rounds April 2006

FTD Prevalence

FTD: Alzheimer’s disease (AD) ratio is 1:1 in those aged 45-65.

FTD is more common that AD below age 60.

FTD spectrum comprises near 15% or more of the total FTD dementia cases.

Frontotemporal dementia subtypes

- Behavior variant (bvFTD): 60% of FTD cases
- Semantic dementia (SD)
- Progressive nonfluent aphasia (PNFA)
- Progressive Supranuclear Palsy (PSP)
- Corticobasal degeneration (CBD)
- FTD with motor neuron disease (FTD-MND)
- ALS/CTE (Chronic Traumatic Encephalopathy)

Boxer AL, Miller BL. Clinical features of frontotemporal dementia. Alzheimer Dis Assoc Disord. 2005;19:S1:S3-4
>50% of FTD subtypes misdiagnosed as primary psychiatric disease


Figure. % of patients initially misdiagnosed prior to ND diagnosis

FTD International Research Criteria

1. Early behavioral disinhibition
2. Early apathy or loss of motivation
3. Loss of emotional recognition, sympathy, empathy
4. Perseverative, compulsive, ritualistic behavior
5. Hyperorality/ dietary change
6. FTD neuropsych profile
7. Frontal and/or anterior temporal atrophy on MRI or other radiologic findings
8. Presence of a known mutation

Brain 2011: 134; 2456–2477
Mendez and Perryman, 2002; Mendez et al., 2007; Rascovsky et al., 2007a; Piguet et al., 2009; the International Behavioural Variant FTD Criteria Consortium (FTDC) issued guidelines for the diagnosis of bvFTD.

Frontotemporal lobar degeneration (FTLD) = Neuropathology of clinical FTD
Pick’s is a FTLD (pathology) not FTD (syndrome)

Abeta positive inclusions composed predominantly of

Absence of tau positive inclusions

Neuronal and glial inclusions Abeta

Neurofibrillary tangles

Absence of inclusions

Pick

Choi

AD

Pick

LSA

FTLD

FTLD+V

FTLD−V

Frontotemporal lobar degeneration (FTLD) = Neuropathology of clinical FTD
Pick’s is a FTLD (pathology) not FTD (syndrome)

FTD damages 3 major networks:
Dorsolateral prefrontal cortex (DLPFC)
Anterior cingulate cortex (ACC)
Orbitofrontal cortex (OFC)

Nonpharmacologic AD prevention

Good physical health = Great aging brain

- Regular physical exercise
- Positive emotions
- Positive relationships
- Limiting chronic stress

“Memory and the Aging Brain” Steven W. Anderson, PhD
Thomas J. Grabowski, Jr. MD The University of Iowa. June 2003
Exercise protects the brain!!

- Aerobic exercise training increases brain volume in aging humans


FDA-approved Medications for Alzheimer’s Disease

Cholinesterase inhibitors (ChEIs)

ChEIs prevent the enzyme destruction of the neurotransmitter acetylcholine (Ach)

- Acetylcholine declines in AD; loss of cholinergic input to the cortex from the basal forebrain.

-Donepezil:
  - selective acetylcholinesterase inhibitor

-Rivastigmine & Galantamine:
  - Inhibitor of acetylcholinesterase & butyrylcholinesterase.

Memantine (Noncompetitive glutamate N-methyl-D-aspartate (NMDA)-receptor blocker)

- FDA approved for moderate-severe AD.
- Blocks the NMDA receptor calcium channels, inhibiting the sustained, low-level influx of excitatory calcium (Ca²⁺) ions into postsynaptic glutamatergic neurons.
- May have a neuroprotective effect by preventing the negative consequences of persistent activation of the neuron.


Investigational drugs and vitamin therapies

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM OF ACTION</th>
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<tr>
<td>AN1792 Vaccine</td>
<td>Abeta immunotherapy</td>
</tr>
<tr>
<td>Tramiprosate alzhemed</td>
<td>Abeta aggregation inhibitor</td>
</tr>
<tr>
<td>Latrepirdine (Dimebon)</td>
<td>Mitochondrial stabilizer – originally anti-histamine</td>
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<tr>
<td>Tarenflurbil (Flurizan)</td>
<td>Gamma-secretase modulator</td>
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<tr>
<td>Semagacestat</td>
<td>Gamma-secretase inhibitor</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Possible membrane lipid modifier</td>
</tr>
<tr>
<td>Docosahexaenoic acid (DHA)</td>
<td>Possible membrane lipid modifier or antioxidant</td>
</tr>
<tr>
<td>B12, B6, Follic Acid, Vitamin E, Omega-3 fatty acids, Ginko Biloba</td>
<td>Multiple theories, negative longitudinal studies</td>
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Statins:

- Elective statin use studied to see if it reduced AD progression
  - Hyperlipidemia promotes Aβ production and deposition in animal models of AD and cholesterol reduction reduce Aβ deposition.
  - Large clinical trials show no efficacy in delaying progression but NO increased AD risk.
  - Feb 2012: FDA warned that statins could cause "reversible memory loss."

The evidence: USE statins for patients with heart or cerebrovascular disease (regardless of AD status)

Siegel GJ et al. Statin therapy is associated with reduced neuropathologic changes of AD. Neurology 2008;71:383-386.

Vitamins ✤ versus diet/ lifestyle ▽

- Vitamin E
  - No difference between placebo.
  - High doses increase stroke risk.
  - Increased relative risk of prostate cancer in men.

- Homocysteine lowering therapy (B-vitamins), Folic Acid B6, B12 – no benefit with supplements
  - The vitamins lower the homocysteine level but little else.
  - B12 and folic acid supplementation did not have any statistically significant effect.

DHA ✨

- Docosahexaenoic acid is an omega3 polyunsaturated fatty acid found in fish.
- Component of synaptic plasma membranes & affects rate of signal transduction ?neuroprotective.
- NEGATIVE RCTs: no effect with supplementation.

Gingko biloba ✨

- Marketed as a supplement that prevents or delays cognitive decline.
- VERY LARGE RCT were negative.
- A numerically greater number of subjects treated with gingko developed dementia as compared to placebo.
Insulin Resistance and AD

- Risk factor for AD: Type II diabetes
  - Impaired insulin signaling in AD, contributing to the neurodegenerative process.
- Exendin-4 (or Exenatide)
  - Phase II trials: testing the effects of novel enzyme-resistant analogues of the insulin-releasing incretin hormone, glucagon-like peptide 1 (GLP-1).
- Intranasal Insulin
  - Delayed memory was improved in the MCI group receiving 20 IU of insulin ($P < .05$). Among insulin-treated participants, no improvement in biomarkers.


Caffeine may decrease level of beta-amyloid in AD transgenic mice

- AD mice received the equivalent of 5 cups coffee/day for 2 months
- End result: caffeinated AD mice performed as well as normal mice
- Caffeinated mice brains showed ~50% reduction in beta amyloid
- Researchers suggested that caffeine suppresses inflammatory changes in the brain that lead to an overabundance of beta amyloid.

Caffeine Reverses Cognitive Impairment and Decreases Brain Amyloid-β Levels in Aged Alzheimer’s Disease Mice; Gary W Arendash, Takashi Mori, Chuanhai Cao, Malgorzata Mamcarz, Alexander Dickson, Kavon Rezai-Zadeh, lin Tan, Bruce A. Chines, Keping Liu, Xiaoyang Lin, Melissa Runfeldt, Alexander Dickson, James Ross-White, Jun Tan, Bruce A. Chines, Xiaoyang Lin, and Huntington Potter; J Alzheimer’s Disease, 2009; 17:3.

Caffeine Suppresses Amyloid-β Levels in Plasma and Brain of Alzheimer’s Disease Transgenic Mice; Chuanhai Cao, John R Cirrito, Xiaoyang Lin, Lilly Wang, Deborah K Verges, Alexander Dickson, Malgorzata Mamcarz, Chi Zhang, Takashi Mori, Gary W Arendash, and Huntington Potter; J Alzheimer’s Disease 2009; 17:3.

Supplements vs. food

“Eat less and exercise more? That’s the most ridiculous fad diet I’ve heard of yet!”
Understanding and treating dementa remains one of the greatest challenges facing all levels of health care.