Recent Developments in the Diagnosis and Treatment of Alzheimer’s Disease

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Overview

• Background on dementia and public health significance of Alzheimer’s disease (AD)

• AD pathology

• Update on AD diagnostics and therapies
  Diagnosis: brain imaging and fluid biomarkers
  Treatment: ongoing clinical trials
  Risk & protective factors
  Lifestyle interventions

• Overview of clinical trial/research study opportunities in MI

• Q & A
Dementia is caused by damage of brain connections that control knowledge, memory, attention, judgment, problem solving, language.
Faces of Dementia
Dr. Alzheimer and Auguste Deter

“When she has to write Mrs. Auguste D, the patient is not able to progress in writing and repeats, ‘I have lost myself’.”

Alzheimer’s disease (AD): most common form of dementia in the elderly (~70%)

progressive memory loss > problems with language, planning, decision-making > behavioral changes; irreversible
AD: a looming crisis

People living with AD:
2018: 5.7M in US (180K in MI)
2025: 7.1M (29% increase), 220K in MI (22% increase)
2050: new case every 30 seconds (~14M in US)

• AD is the 6th leading cause of death in US and only disease that cannot be prevented or cured

• AD is the most expensive disease in US
  - $277B in 2017 - 2/3 paid by Medicare and Medicaid
  - Costs projected to reach $1.1 trillion in 2050
  - 2018: 16.1M caregivers provided 18.4 billion hours of unpaid care

NO TREATMENT TO SLOW IT DOWN!
AD is a women’s health issue

Women are at the epicenter of the Alzheimer's epidemic.

1 in 6
In her 60s, a woman's estimated lifetime risk for developing Alzheimer's is 1 in 6. For breast cancer it is 1 in 11.

2/3
Almost two-thirds of Americans with Alzheimer's are women.

2.5
There are 2.5 times more women than men providing intensive “on-duty” care 24 hours a day for someone with Alzheimer's.

60%
More than 60 percent of Alzheimer's and dementia caregivers are women.

Critical need to research and understand sex differences in AD
Ethnic disparities in AD

- African-Americans are twice as likely, and Hispanics are 1.5 times as likely, to have AD during their lifetimes compared to Caucasians.

- Possible reasons: genetics, education, mid-life risk factors such as metabolic syndrome (food deserts), access to healthcare (socioeconomic, trust, language barriers).

- Critical need to research and understand these disparities.
AD research: brain basics

A "neuron forest" in the brain

Brain cells are called NEURONS

100 billion neurons in the brain make 100 trillion connections!

Frontal lobe: "executive function" and behavior
Parietal lobe: integrates "input" and "output"
Temporal lobe: memory and language
Brainstem: attention/vigilance "autonomic function"
Occipital lobe: vision
Cerebellum: balance and coordination

Brainstem:
Attention/vigilance
"Autonomic function"

A "neuron forest" in the brain

Neurons "talk" to each other by using connections called SYNAPSES

100 billion neurons in the brain make 100 trillion connections!
AD: degeneration of brain areas that control memory, attention, language, and "executive" functions.
I’ve budgeted myself $85K for year 1 ($65K to subcontract, $150K total) and $65K for year 2 ($65K to subcontract, $125K total).

**AD brain:** amyloid “plaques” build up between neurons

“thickened miliary foci”

Plaques in the frontal lobe
*(made of amyloid, also called β-amyloid or Aβ)*
genes that cause early-onset AD lead to more amyloid plaques in the brain

Table. Genetic Factors Predisposing to Alzheimer Disease: Relationships to the β-Amyloid Phenotype

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene Defect</th>
<th>Phenotype</th>
</tr>
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<tbody>
<tr>
<td>21</td>
<td>β-Amyloid precursor protein</td>
<td>Increased production of all β-amyloid proteins or β-amyloid protein 42</td>
</tr>
<tr>
<td></td>
<td>mutations</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Apolipoprotein E4 polymorphism</td>
<td>Increased density of β-amyloid plaques and vascular deposits</td>
</tr>
<tr>
<td>14</td>
<td>Presenilin 1 mutations</td>
<td>Increased production of β-amyloid protein 42</td>
</tr>
<tr>
<td>1</td>
<td>Presenilin 2 mutations</td>
<td>Increased production of β-amyloid protein 42</td>
</tr>
</tbody>
</table>

Alzheimer cells

healthy cells
AD brain: neurofibrillary “tangles” build up inside of neurons

“peculiar fibrillary changes of the nerve cells”

Tangles in the hippocampus (made of tau)

Most tangle-bearing neurons eventually die in AD
AD diagnosis and therapy: targeting the “preclinical” stages

AD may begin decades before symptoms!
AD diagnostics: the key to an effective therapy

World Wide AD Neuroimaging Initiative (WW-ADNI)

Funded by the NIH partnering with:

- Help predict and monitor the onset and progression of AD
- Brain imaging and collection of cerebrospinal fluid and blood samples = biomarkers
- Establish globally recognized standards to diagnose and treat AD
- Share data across the international research community
AD diagnosis: brain imaging

We can now use positron emission tomography (PET) imaging to examine both plaques (amyloid) and tangles (tau) in normal elderly to see who may have “preclinical AD”.

MRI shows areas of brain “thinning” in people who developed AD 5-10 years later.

Amyloid PET scans are often “positive” before tau or MRI scans.

PCAD?
Amyloid imaging as a first-line screen?

- FDA approved (2012) in cognitively impaired individuals
  - To assist with differential dementia diagnoses
- Not yet recommended for clinical use with cognitively normal elders as a “preclinical” biomarker
  - Unclear predictive value
AD diagnosis: amyloid and tau in the cerebrospinal fluid

People who convert to AD display:
- rapid annual decreases in CSF amyloid
- rapid annual increases in CSF tau

This occurs over several years prior to clinical symptoms
Recent Japanese study in *Nature* suggests utility of blood test for amyloid.

Would be much cheaper, easier to administer than amyloid PET scan, and much less invasive than collecting CSF.

Latest data: levels of a protein called Neurofilament light (NFL) increase in the blood as people begin showing signs of mild cognitive impairment and increase further as AD begins.
Diagnosing preclinical AD: best chance for effective therapy

Current thinking: amyloid changes > tau changes and brain thinning > cognitive symptoms decades after initiation of disease
AD therapies: the amyloid story so far...

Special “AD mice” have amyloid plaques & perform poorly in memory mazes > the AD mice are vaccinated with antibodies to amyloid > this treatment removes the plaques and improves memory
You can cure AD in a mouse!

Removing plaques in AD patients hasn’t worked too well:

<table>
<thead>
<tr>
<th>Baseline MMSE (points)</th>
<th>Aβ1753 dose (μg)</th>
<th>Mean antibody response (ELISA units)</th>
<th>Evidence of Aβ plaque removal</th>
<th>Aβ load</th>
<th>Braak tau stage</th>
<th>Survival time (months)</th>
<th>MMSE before death (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>50</td>
<td>1.500</td>
<td>None</td>
<td>2.96%</td>
<td>V</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>15</td>
<td>170</td>
<td>1.390</td>
<td>None</td>
<td>3.02%</td>
<td>VI</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>21</td>
<td>59</td>
<td>1.110</td>
<td>Intermediate</td>
<td>0.75%</td>
<td>VI</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>32</td>
<td>1.40/2</td>
<td>Intermediate</td>
<td>6.65%</td>
<td>VI</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>59</td>
<td>1.1/2</td>
<td>Intermediate</td>
<td>2.31%</td>
<td>VI</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>32</td>
<td>1.4/3</td>
<td>Intermediate</td>
<td>1.81%</td>
<td>VI</td>
<td>63</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>59</td>
<td>1.4/3</td>
<td>Very extensive</td>
<td>0.12%</td>
<td>VI</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>59</td>
<td>1.6/70</td>
<td>Very extensive</td>
<td>0.35%</td>
<td>VI</td>
<td>64</td>
<td>0</td>
</tr>
</tbody>
</table>

MMSE: Mini-Mental State Examination. *None:no or nearly no process of plaque removal; intermediate: moderate/partial removal of plaques; very extensive: virtually complete removal of plaques. OF: otherwise healthy, mean age: Braak stage VI, course stage V. Patient died suddenly after a period of delirium and anorexia.

Table 1: Aβ plaque removal and clinical characteristics of participants who had received Aβ1753 and who had post-mortem neuropathology.
Pfizer and others pulling out of AD R&D after amyloid antibody failures
Aducanumab: early success brings renewed hope for amyloid antibodies as a therapy for AD

Biogen: 165 mild AD patients treated for 1 year. All enrolled were Amyloid PET+. 4 dose groups or placebo.

Results suggest amyloid plaque removal AND better memory scores.

New trials ongoing with MCI and early-stage subjects.

Amyloid PET scans

Effect of Aducanumab on Clinical Decline as Measured by MMSE (Exploratory Endpoint)
AD therapy: stopping plaques before they start

- Amyloid may harm the brain before it forms plaques in the brain.
- New drugs (BACE inhibitors) prevent the production of amyloid.
- In “AD mice”, these inhibitors stop plaques and improve memory.
- 2 clinical trials from Merck and Janssen were discontinued due to liver problems.
- AZD3293: 2 year clinical trial with 1550 early AD patients, sponsored by Eli Lilly and AstraZeneca (ends May 2019).
AD therapy: targeting tangles

- Tangles correlate with the progression of AD better than plaques.
- Three clinical trials were halted in 2016 for missing primary endpoints (e.g., they did not slow cognitive decline).
- New tau antibody trials are underway – AbbVie-sponsored trial running 2016-2020, 400 people with early stage AD, 3 doses tested.

Tangles in AD

TRx0237 prevents the formation of tangles in “AD mice”
Dozens of potential AD meds in the pipeline

- A new drug for Alzheimer's hasn't been approved in US since 2003

- Three dozen new drugs in various stages of clinical trial testing - may reach the market within the next 5 years

- Some drug candidates include anti-diabetic and anti-inflammatory drugs & drugs to boost norepinephrine and serotonin (similar to anti-depressant or anti-ADHD drugs)
Prevention strategies for AD: modifying risk factors

**Lifestyle factors**

- **education**: life-long learning = cognitive reserve
- **diet and exercise**: cardiovascular disease and diabetes can double the risk for cognitive impairment
- **social activity**: social isolation doubles risk for cognitive impairment
- **chronic stress**: doubles risk for cognitive impairment

**age**

- 85+ years, 38%
- 75-84 years, 44%
- 65-74 years, 15%
- <65 years, 4%

**female sex**

- Men: 12.2%
- Women: 15.1%

- Men: 18.2%
- Women: 20.1%

- Men: 29.4%
- Women: 30.4%
The Lancet Commission: one third of dementia may be preventable

- International panel of 24 experts reviewed the literature and found 9 modifiable risk factors across the lifespan that would collectively reduce dementia risk by ~30-35% (caveat: specific diets not included)
- Early life: Staying in school until you're at least over the age of 15
- Mid-life (~45-66): hypertension, obesity, hearing loss
- Later life: depression, diabetes, physical inactivity, smoking, low social contact

Specific recommendations
- expand childhood education, improve retention
- vigorous treatment of hypertension and maintaining overall good health through diet and exercise
- stop smoking
- manage depression, social activity, and hearing loss
Hearing loss and cognitive change?

• 2017 study by Wisconsin Registry for AD Prevention

• Of 783 people in their 50’s, those w/ diagnosis of hearing loss performed worse on a range of tests of cognitive skills

• Four years later, those w/ hearing loss over 3X likelier to be diagnosed with MCI

• Identification and treatment of hearing loss might reduce AD risk, enhance social and intellectual engagement

• Only 30% of 70+ who need a hearing aid have ever used one
Proactive resilience: targeting health conditions linked to AD

- Metabolic syndrome:
  - Hypertension
  - High blood sugar, A1C > diabetes
  - High blood cholesterol and triglycerides (mainly from saturated and trans fats/”hydrogenated oils”) > hyperlipidemia
  - Genetics, yes, but much is self-inflicted…

- The “Smorgasbird” is probably awesome, but probably not great for our brains!
  - Countless human epidemiology and animal studies
  - Metabolic syndrome: ~doubles risk for cognitive impairment

**TAKE HOME MESSAGE:** “what’s good for your heart is good for your brain”
Mediterranean diet as a guideline

Percentage of US population that follows healthy diet and exercises daily.............7%! (Xu et al., 2013)
PREVIMED study: Prevention with Mediterranean diet

- 2,258 older individuals without dementia
- Assessed for adherence to Mediterranean diet
- Over an average of 4 years of follow-up, 262 persons developed AD
- “High adherence” to diet had 40% reduction in risk compared to “low adherence”
- Slower rates of MCI to AD transitions for both “high” and “middle” adherence groups compared to “low adherence”

(Scarmeas et al, 2006)
The MIND diet

MIND diet puts together the best brain foods of the Mediterranean diet and the salt-reducing DASH diet

MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay
DASH: Dietary Approaches to Stop Hypertension

Simple, plant-based cooking with emphasis on fruits & vegetables (especially leafy greens), whole grains, beans, seeds, some nuts, extra virgin olive oil. Refined sugar or flour and saturated fats such as butter (which promote oxidative stress and inflammation) are rarely consumed
Prevention via MIND and similar diets

2 large population based studies on diet and dementia risk

1. In ~6,000 healthy older adults in the Health and Retirement Study, those who closely adhered to the MIND/Med diet had a ~35% lower chance of cognitive impairment; moderate adherents lowered risk by ~20%

2. In ~7,000 older women in the Women’s Health Initiative, over ~10 years, those who closely followed the MIND diet had a ~35% reduction in risk of AD. Even moderate adherents displayed ~20-25% reduction in AD risk
Exercise and cognitive health:
1 year walking program for mild AD patients

Winchester et al., 2013
6 month walking program for AD patients

| Table 2. Biomedical and Cognitive Results
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>WG (Walking Group)</td>
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<tr>
<td></td>
<td>Pre</td>
</tr>
<tr>
<td>6WT (m)</td>
<td>245 ± 31</td>
</tr>
<tr>
<td>Glycemia (mg·dL⁻¹)</td>
<td>94 ± 5</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>132 ± 10</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>84 ± 5</td>
</tr>
<tr>
<td>Barthel (0-100)</td>
<td>34 ± 4</td>
</tr>
<tr>
<td>MMSE (0-30)</td>
<td>13 ± 2</td>
</tr>
</tbody>
</table>

Abbreviations: 6WT, 6 minute walk test; MMSE, Mini-Mental State Examination; ANOVA, analysis of variance.

a Two-way ANOVA.
b P < .05 (within group).
c P < .05 (between groups).

Venturelli et al., 2011
Dr. Eric Kandel: 2000 Nobel Prize for discovering how memories form

*Exercise releases two factors in the brain:*

- **Brain-derived neurotrophic factor (BDNF):** key support for neurons in hippocampus (short/long term memory)

- **Osteocalcin:** bone hormone improves age-related memory loss in animal models
The FINnish GERiatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)

- Large Finnish lifestyle intervention trial (n = 1260) with older adults age 60-77
- Seven year study
- 2-year intervention including:
  - Nutritional guidance
  - Physical exercise training
  - Computer-based cognitive training
  - Monitoring of vascular risk factors
  - Controls (no intervention)
- Intervention group scored better in memory, processing speed, and executive functions.

(Ngandu et al., 2015)
U.S. POINTER Study: U.S. study to PrOtect through a lifestyle INTErvention to Reduce risk

- No approved medications to date have produced results as strong as the FINGER Study, so there is a pressing need to test the effectiveness of multicomponent lifestyle interventions

- $20M, 2-year trial sponsored by Alzheimer’s Association to test interventions to prevent cognitive decline and dementia in 2,500 healthy older adults at increased risk for cognitive decline (e.g., metabolic disorders)

- Recruitment began in 2018

4 primary components of the lifestyle intervention are:

- Physical exercise
- Nutritional counseling and modification
- Cognitive and social stimulation
- Improved self-management of medical conditions

www.alz.org/us-pointer
Clinical trials and research studies in MI

MSU: Andrea Bozoki, MD

https://neurology.msu.edu/CoGeNT/

Clinical trials (e.g., amyloid antibodies)
Lifestyle intervention studies
Observational studies (ADNI)
Caregiver studies

http://alzheimers.med.umich.edu/research
734-936-8803

www.alz.org/TrialMatch (search Michigan)
Acknowledgements
Q & A Time

Thank you very much!
<table>
<thead>
<tr>
<th>Lowering risk through lifestyle!</th>
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<tbody>
<tr>
<td>Break a Sweat</td>
</tr>
<tr>
<td>Fuel Up Right!</td>
</tr>
<tr>
<td>Hit the Books!</td>
</tr>
<tr>
<td>Catch Some Zzz’s</td>
</tr>
<tr>
<td>Butt Out!!</td>
</tr>
<tr>
<td>Take Care of Your Mental Health!</td>
</tr>
<tr>
<td>Follow Your Heart</td>
</tr>
<tr>
<td>Buddy Up!</td>
</tr>
<tr>
<td>Heads Up!</td>
</tr>
<tr>
<td>Stump Yourself!</td>
</tr>
</tbody>
</table>

*Image credit: Michigan State University College of Human Medicine*
## Normal aging vs. dementia

<table>
<thead>
<tr>
<th></th>
<th>Normal Aging</th>
<th>Possible Indicator of Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory Loss</strong></td>
<td>Temporarily forget names or where you left your keys.</td>
<td>Difficulty remembering familiar names, places, or recent or important events.</td>
</tr>
<tr>
<td><strong>Disorientation</strong></td>
<td>Forget the day of the week or why you entered a room.</td>
<td>Get lost on your own street or forget where you are and how to get home.</td>
</tr>
<tr>
<td><strong>Challenged by Mental Tasks</strong></td>
<td>Make a mistake when balancing a checkbook.</td>
<td>Unable to complete tasks that may be familiar to you such as balancing a checkbook or following a recipe.</td>
</tr>
<tr>
<td><strong>Difficulty Completing Activities of Daily Living</strong></td>
<td>Sometimes need assistance with an electronic device.</td>
<td>Need assistance with brushing teeth, getting dressed or using the phone.</td>
</tr>
<tr>
<td><strong>Trouble Using Words Appropriately</strong></td>
<td>Occasionally struggle to find the right word.</td>
<td>Difficulty completing sentences and following directions/conversations.</td>
</tr>
<tr>
<td><strong>Poor Judgment</strong></td>
<td>Make questionable or debatable decisions at times.</td>
<td>Unsure how to dress or giving money to solicitors excessively.</td>
</tr>
<tr>
<td><strong>Changes in Mood and Personality</strong></td>
<td>Fatigued by obligations or irritable when a routine is disrupted.</td>
<td>Increased suspicion, withdrawal and disinterest.</td>
</tr>
</tbody>
</table>
Brain changes and symptoms over time

**Mild Cognitive Impairment**
- Duration: 7 years
- Disease begins in Medial Temporal Lobe
- Symptoms: Short-term memory loss

**Mild Alzheimer's**
- Duration: 2 years
- Disease spreads to Lateral Temporal & Parietal Lobes
- Symptoms include:
  - Reading problems
  - Poor object recognition
  - Poor direction sense

**Moderate Alzheimer's**
- Duration: 2 years
- Disease spreads to Frontal Lobe
- Symptoms include:
  - Poor judgment
  - Impulsivity
  - Short attention

**Severe Alzheimer's**
- Duration: 3 years
- Disease spreads to Occipital Lobe
- Symptoms include:
  - Visual problems
Vascular dementia: quick facts

~20% of all dementias – second most common often co-occurs with AD = “mixed dementia”

mainly caused by strokes

risk factors: high BP, high cholesterol, diabetes, “hardening of the arteries”

loss of “executive function”: planning, decision making, problem solving; confusion; memory and language

Blood (oxygen) supply to the brain

strokes cut off oxygen supply to parts of the brain
Lewy body dementia: quick facts

~10-15% of all dementias

Genes and risk factors unknown

Injured neurons contain “Lewy bodies” – located in many areas throughout brain, brain does not shrink

Progressive loss of memory, language, decision-making (Alzheimer’s); movement problems (Parkinson’s), and hallucinations

Frederic Lewy and Alzheimer, 1900s

“Lewy bodies”

“draw this” normal elderly AD LBD
Frontotemporal dementia: quick facts

- 5-10% dementias - linked to several genetic mutations
- Injured neurons contain “Pick bodies”
- Caused by major shrinking of frontal and temporal lobes - requires MRI for accurate diagnosis
- Major changes in personality and behavior, loss of ability to speak, write, or understand language, movement problems

Arnold Pick, MD, 1892

“Pick bodies”

Frontal lobe: “executive function” and behavior

Temporal lobe: memory and language

“Pick bodies”

Frontal lobe: memory and language

Temporal lobe: memory and language

NML

FTD