Alzheimer’s Disease Update: From Treatment to Prevention

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Alzheimer’s Disease

- Most common cause of dementia (50 – 70%)
- Marked by early memory impairment, executive dysfunction

Alzheimer’s Facts

- 5.2 million Americans have AD in 2008
- One in eight (13 percent) over 65 have AD
- Every 71 seconds someone develops AD
- $148 billion in direct and indirect costs to Medicare, Medicaid, and businesses.
What is Dementia?

1. Decline in cognition
   • Memory
   • Executive Function: Planning / Organization
   • Language
   • Orientation

2. Interferes with everyday function
Causes of Dementia

- Alzheimer’s Disease: 50 - 70%
- Dementia With Lewy Bodies: 15%
- Vascular Dementia: 10%
- Frontotemporal Dementia: 5%
- Other
Where are we now?

• We can diagnose Alzheimer’s disease accurately and early

• Alzheimer’s disease is treatable
Diagnosing AD

• Detailed History
  – Characteristics and pattern of changes
  – Importance of informant / caregiver

• Physical Examination

• MRI or CT to r/o structural process

• Lab work: TSH, B12
  – Currently, no brain scan or blood test can replace the clinical evaluation
Early Cognitive Changes in Alzheimer’s Disease

**Memory Loss**
- Forgetfulness (conversations; appointments; medicines; names)
- Repetition of questions, statements
- Misplacing items

**Executive Dysfunction**
- Managing household finances
- Driving
- Meal preparation
- Operating appliances
Alzheimer’s is a Treatable Disease
Approved AD Therapies

• Two classes of approved medications
  – Cholinesterase inhibitors → increase acetylcholine levels
    • Donepezil
    • Galantamine
    • Rivastigmine
  – NMDA antagonist
    • Memantine
Effect of Medications on AD Course

Initiate Medications

Donepezil
Galantamine
Rivastigmine

Cholinesterase inhibitors

Namenda

Time

Cognitive Abilities
Where are we now?

• We can diagnose Alzheimer’s disease accurately and early

• Alzheimer’s disease is treatable
85 years old - MMSE 2/30 - Having difficulty with making a snack, choosing clothes to wear, discussing current events 2 years later

2 years later
Amyloid Plaques & Tangles
New Age of Molecular Imaging: Plaque and Tangle Imaging

PET Scanner

Plaques and Tangles

Not elevated

Elevated
The Amyloid Hypothesis

“Amyloid plaques cause the disease”

But we do not know if amyloid is the SMOKE OR FIRE?

Amyloid Production

Toxic effects?

Cell Death

Remove Amyloid
Trials are Continuing but Early Failures are Mounting for Amyloid-Based Approaches

- **2005: AN-1792**: active Abeta vaccination (Phase 2)
  - 300 AD participants – halted due to meningoencephalitis
  - Fewer Abeta plaques in brain despite dementia progression

- **2008: Flurizan** (tarenflurbil): reduces amyloid levels
  - 1649 mild AD participants: no evidence of efficacy

- **2009: Alzhemed** (tramiprosate): inhibits Abeta formation and deposition
  - 1052 AD participants: no evidence of efficacy

- **2010: Semagacestat**: gamma secretase inhibitor
  - 2600 AD participants: halted early due to greater rates of progression in treated participants

- **2012: Bapineuzumab**: antibody for amyloid
  - No effect in those with ApoE4 genetic risk
Promising Results from Phase 1 Trial of Anti-Amyloid Drug (Aducanumab)

Amyloid Reduction

Promising Results from Phase 1 Trial of Anti-Amyloid Drug (Aducanumab)

Slower Cognitive Decline

Thinking Beyond Amyloid

- Amyloid (plaques)
- Tau (tangles)
- Vascular (low blood flow)
- Metabolism
  - Insulin resistance
  - Mitochondria
- Genetics
Treatment Trials:
KU ADC Clinical Trial Unit

- **Anti-Amyloid**
  - Solanezumab (Eli Lilly)
  - Aducanumab (Biogen)
  - Azeliragon (vTV)
- **Anti-Tau**
- **Neuroprotection**
  - TCAD study (Toyama)
  - Bryostatin (Neurotrope)
- **Metabolic Studies (KU led)**
  - Metabolic approaches (Diet, Exercise, OAA, S-equol)
80 yo with 2 years of progressive cognitive decline

- Forgetfulness
- Geographically challenged
- Broad but mild cognitive deficits in global cognition, memory, and executive function
  - MMSE 23; LMI 5, LMII 2, Trails 220, Free recall 7,5,2
- Enrolled in clinical trial for AD
MRI
Diffuse Amyloid Accumulation
Severe Tau Pathology in Limbic and Neocortical Association Areas
Caveats for AD Biomarkers

- Dichotomous biomarker test result ("positive" or "negative"), but AD is characterized by a continuous pathobiological process
  - Ambiguous or indeterminant results will occur
- Must standardize CSF and imaging biomarkers and validate them (sensitivity and specificity), particularly in practice settings
- Varying access to biomarkers in the community
- Reimbursement?
Where are we going?

• Diagnose before the onset of symptoms

• Halt or reverse the disease process
Preventing Alzheimer’s: What do we really know?

• NIH Panel April 2010
  – Insufficient evidence to support broad use of interventions to prevent dementia.
  – Need for large-scale studies including randomized clinical trials
Preventing Alzheimer’s: What do we think is true?

Many AD risk factors are modifiable

– Risk factors
  • Blood pressure
  • Cholesterol
  • Stroke
  • Diabetes
  • Obesity

– Protective factors
  • Education / Occupation
  • Exercise
Limitations of Previous Studies

• Direct evidence is lacking
  – Observational studies vs. randomized trials

• Reverse causation?
  • Does exercise make us smarter?
  • Or do more smart people exercise?

  – Disease may influence physical activity rather than physical activity influencing disease
Exercise in the Fight Against AD

• Our studies suggest
  1. Exercise has brain benefits, even at low doses
  2. Exercise may slow AD (disease modification)
  3. Optimal target is to increase aerobic capacity

• But, we still need rigorous scientific data to
  1. Prove brain benefits
  2. Understand magnitude of effects
    • What kind is best and how much?
  3. Understand mechanisms
Exercise Testing – Fitness or Aerobic Capacity
Higher Aerobic Fitness is Associated with Less Brain Atrophy

Aerobic Capacity associated with less atrophy in brain areas affected by AD

Burns et al, Neurology, 2008

Honea et al, Alz Dis Assoc Dis, 2009
Alzheimer’s Disease Exercise Program Trial (ADEPT)

Does Exercise Slow AD Progression?
1. Cognition and function
2. Brain atrophy (MRI)
3. Physical Function / Body composition
Aerobic Exercisers Maintained Functional Ability

Over 6 months
- AEx group maintained (+1.5)
- ST group declined (-4.5)

normal course of AD equates to loss of 1 point per month

Morris, Vidoni et al, PLOS One 2017
Changing Fitness Levels Related with Changes in Memory

Morris, Vidoni et al, PLOS One 2017
Frequent, Brisk Walks May Aid Those With Early Alzheimer’s

March 1, 2017

Aug 12, 2015

The Right Dose of Exercise for the Aging Brain

By GRETCHEN REYNOLDS

AUGUST 12, 2015 5:31 AM

91 Comments
Any is better than none!
(And more is even better)
What’s Good for the Heart Is Good for the Brain!

• It’s never too late!
• Sit less, move more!
  – Not necessary to achieve a “threshold” of 150 minutes a week or 10,000 steps
  – Even 75 minutes a week has benefits
  – Reduce prolonged sitting

• Heart Healthy or Mediterranean Diet
Exercise your brain!

• Mentally stimulating activities
  – Give your neurons a workout!
    • Lectures, social activities, reading, puzzles
    • There is nothing special about crosswords!

• Scientific data is limited
  – Improvement at what you practice…but
  – Not yet clear that your daily activities improve
  – But it can’t hurt!
Where are we going?

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- Halt or reverse the disease process
New Age of Molecular Imaging: Plaque and Tangle Imaging

PET Scanner

Plaques and Tangles
Detecting AD Before Symptoms?

Elevated Amyloid

Cognitively normal

3 years later, Alzheimer dementia

Mark A. Mintun and John C. Morris
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Brain Amyloid without Symptoms: What does it mean?

• 30% of healthy adults have brain amyloid
  – Not a diagnosis of AD
  – Not all develop AD
• Risk factor for developing AD
  • Risk likely spread out over 10 to 20 years
KU ADC
Alzheimer’s Prevention Program

– Launched in late 2012 to usher in the new era of prevention trials

1. Assess Alzheimer’s risk in healthy older adults
2. Test prevention strategies
   – Exercise
   – Anti-amyloid strategies
   – Vascular risk reduction
New Era of Prevention Trials

• Window of opportunity
  – Identify Alzheimer’s changes prior to onset of symptoms

• Prevention Strategies
  – Exercise
  – Anti-amyloid strategies
    • Anti-amyloid Treatment in Asymptomatic AD
      – Solanezumab
A4 Study:
Anti-Amyloid Treatment in Asymptomatic Amyloidosis

- Large national prevention trial
- Older adults (age 65-85) at higher risk of AD (by amyloid PET scan)
- Drug study of anti-amyloid drug (solanezumab) or placebo for 3 years
- 10 times bigger than APEX
  - Screening 10,000 to find 1,150 at-risk individuals
Alzheimer’s Prevention Program
Exercise Trial (APEX)

• Does 1 year of aerobic exercise
  – Reduce brain amyloid levels
  – Slow brain shrinkage
  – Improve memory and thinking

• We need you!
  – We need 400 cognitively normal individuals
    • Identify 100 individuals at higher risk of AD
New Studies

- **rrAD**
  - Vascular risk reduction strategies
  - 2 year study
  - N = 640 hypertensives
    - N = 160 in KC

- **IGNITE**
  - Definitive RCT of exercise and brain health
  - 1 year study
  - N = 640 older adults
    - N = 213 in KC
Translating biomedical research findings into everyday strategies for Alzheimer’s prevention and brain health
Collaboration with the YMCA of Greater Kansas City and Garmin

• Clinician prescribed program
• Testing health effects at 12 and 52 weeks
  » Fitness, insulin, glucose, cholesterol, body composition
• NIH-funded clinical trial – set to start in June 2018
Where are we going?

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Here’s how you can help...

• Volunteer for a study
• Spread the word
• Stay informed
• Donate