Healthy Brain Aging

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What can you expect from this seminar?

• To gain a basic understanding of the differences between normal aging and Alzheimer’s disease

• To be able to name factors that increase or decrease risk for memory loss with aging

• To identify one practical thing you can do or change in your life to promote healthy brain aging

• To learn about local Alzheimer’s research
What exactly is Alzheimer’s Disease (AD)?

• AD is the most common form of dementia

• Dementia is the general term for conditions causing cognitive decline that interfere with day-to-day life
  
  — Other types include: Lewy body dementia, Frontal temporal dementia, Vascular dementia

• Typical symptoms of AD include loss of short-term memory, confusion, and disorientation
When was AD first recognized?

- Alzheimer’s disease was first described by Alois Alzheimer in 1906
- Currently, more than 5.4 million people in the U.S. have AD
- This number is expected to triple in the next 30 years

How is AD different from normal aging?

In normal aging, nerve cells in the brain are not lost in large numbers.

In contrast, AD causes many nerve cells to stop functioning, lose connections with other nerve cells, and die.

From http://www.ahaf.org/alzdis/about/cross_sectioncompareBorder.jpg
What changes in the AD brain?

**Plaques** = clumps of β-amyloid protein outside of neurons

**Tangles** = abnormal tau proteins twisted together inside of neurons

**Decrease in Acetylcholine**, the chemical involved in memory

**Increase in Oxidative Stress**

From: http://www.ahaf.org/alzdis/about/AmyloidPlaques.htm
What are risk factors for Alzheimer’s disease?

• Age

• Genetics
  – Early Onset (30-60 yr)
    ▪ Rare (~5%)
  – Late Onset (>60 yr)
    ▪ APOε4
      ~40% of AD patients
      ~25% of population
My Story
Brain Health vs. Clinical Symptoms

- There is a disconnect between identified disease changes in the brain and the severity of clinical symptoms
- Some people can have large numbers of brain changes (plaques) without a deficit in cognitive function
- What factors are involved with this disconnect?
Potentially Protective Lifestyle Choices

- Higher education
- Regular exercise
- Healthy diet
- Intellectually challenging leisure activity
- Socially integrated lifestyle
- Reduction of cardiovascular risk factors
Physical Activity

- Individuals that are more physically active have reduced risk of cognitive decline and dementia
- Physical activity increases blood flow to the brain
- Physical activity increases BDNF, a nerve growth factor that protects brain cells
- Example: aerobic exercise, walking, etc.
Physical Activity

• In late adulthood, the hippocampus (part of the brain involved in memory) shrinks, resulting in impaired memory and increased risk of dementia

• In adults who are fit, the hippocampus is larger

http://library.thinkquest.org/C0110291/images/brain1_large.gif
Physical Activity

• Research Question – Can aerobic exercise increase the size of the hippocampus and improve memory?

• Randomized control trial - 40 min, 3 days per week for 1 year
  – Aerobic exercise – walking in targeted heart rate zone
  – Stretching – muscle toning, balance, yoga

Erickson et al. | PNAS | February 15, 2011 | vol. 108 | no. 7 | 3017–3022
Physical Activity

• 1-2 year reversal of age related loss of hippocampal volume

  Aerobic exercise ↑ 2%   Stretching ↓ 1.4%

Hippocampus

• Associated with ↑ aerobic fitness, ↑ BDNF levels, ↑ memory performance
Mental Activity

• Individuals with higher levels of mental activity have:
  – About half the risk of developing dementia
  – A reduced rate of cognitive decline

• Examples: cognitive tasks, sensory stimulation, music, art
The Adaptable Brain

• Research has shown that despite injury, the brain has a tremendous ability to re-organize and restore function

• External events/experiences
  → Changes in the brain
    ↑ Numbers of brain cells
    ↑ Connections between brain cells

• Cognitive Reserve Theory
Social Activity

- Example: connections with friends & family
- Individuals that have low participation in social activities and less social support have an increased risk of dementia
Nutrition

• Example: brain healthy foods
• Evidence has shown a lower risk of dementia with:
  – Adherence to a Mediterranean diet (healthy fats, fruits, vegetables, fish)
  – Greater intake of fruits/veggies
Nutrition

- Eating fish has been linked to a reduced risk of Alzheimer’s disease.
- Fish highest in omega-3 fatty acids are salmon, herring, mackerel, sardines, or lake trout.
- There are also plant sources of omega 3 including avocado, olive oil, almonds, walnuts, and sunflower seeds.
Nutrition

• Studies also suggest benefits of foods such as green tea, curcumin, dark chocolate, red wine
• Studies of vitamins and supplements, such as omega-3 fatty acids, have not yet been shown to have beneficial effects for treatment or risk reduction of dementia
MIND Diet

- MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay
  (DASH = Dietary Approaches to Stop Hypertension)

- Prospective study of 923 participants, ages 58-98 years, followed on average 4.5 years, comparing the effect of 3 diets on the incidence of Alzheimer’s disease
The right foods could lower your risk of dementia and improve your brain function

**MIND DIET**

- **Green Leafy Veggies**
  - ≥ 6 servings/week
- **Nuts**
  - ≥ 5 servings/week
- **Fish**
  - ≥ 1 servings/week
- **Wine**
  - 1 serving day
- **Legumes**
  - ≥ 3 servings/week
- **Berries**
  - ≥ 2 servings/week
- **Poultry**
  - ≥ 2 servings/week
- **Olive oil**
  - Primary oil
- **Vegetables**
  - ≥ 1 servings/day
- **Whole grains**
  - ≥ 3 servings/day

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Adherence to the diets was significantly associated with lower risk of developing Alzheimer’s disease.

- High adherence – 53% reduction in risk
- Medium adherence – 35% reduction in risk
- Low adherence
Cardiovascular Risk Factors

- Examples: obesity, high cholesterol, diabetes, high blood pressure
- Are associated with an increased risk of dementia
- Much evidence supporting association of protection against dementia in elderly with medications for lowering of blood pressure, treatment of diabetes, lowering of cholesterol
Take Home Messages

• Healthy lifestyle behaviors show promise for delaying cognitive decline associated with aging.

• Take a moment to identify one small thing you can do to promote healthy brain aging.
Finding new ways to identify, treat and prevent memory loss

How are lifestyle choices and stress associated with memory changes as we age?
What treatments are currently available for AD?

**Mild to Moderate AD:**
- Aricept (Donepezil): 1996
- Exelon (Rivastigmine): 2000
- Razadyne (Galantamine): 2002
  - formally named Reminyl

All inhibit acetylcholinesterase, an enzyme that breaks down the neurotransmitter, acetylcholine involved in memory, thought and judgement.

**Moderate to Severe AD:**
- Namenda (Memantine): January 2004

Inhibits the over activity of glutamate, a neurotransmitter, thought to contribute to neuronal dysfunction and death in AD.

**While all of these medications improve neuronal function, none of them stop or reverse AD**

[HealthPartners Center for Memory & Aging]

[www.clinicaltrials.gov]
Why is it so hard to develop treatments for brain disease?

• The blood-brain barrier (BBB) protects the brain but also prevents access of medications.

• High doses of drugs or surgical intervention have been used in attempts to overcome the BBB.

• We discovered a simple non-invasive method of bypassing the BBB which targets therapeutics to the brain – INTRANASAL delivery.

• Intranasal drugs are rapidly delivered to the brain along the olfactory nerves involved in smell and the trigeminal nerves.
How is AD related to diabetes?

• AD patients have reduced uptake and utilization of blood sugar
• Brains of AD patients have reduced levels of insulin
• People with diabetes have twice the risk of developing Alzheimer’s
• Alzheimer’s disease as “diabetes of the brain” or a type-3 diabetes

Intranasal Insulin

- Intranasal insulin rapidly reaches the CSF and does not alter blood levels of insulin or glucose
- Intranasal insulin improves memory in Alzheimer’s patients (Acute, 21 days, 4 months)
  - Increased ability to retain verbal information after a delay (delayed recall) compared to placebo and significantly improved attention and functional status
- Intranasal insulin improves memory in healthy adults
  - 8 weeks of treatment improved memory and mood
- Current 6 month trial underway
Deferoxamine (DFO)

- chelator of Fe, Al, and Cu with a strong Fe III binding constant ($10^{31}$)
- FDA approved for the treatment of iron overload
- rapidly eliminated from the blood and does not readily cross the blood-brain barrier

Iron accumulates in the AD brain and leads to oxidative stress, one of the biological pathway implicated in the pathology of Alzheimer’s disease. DFO could bind and remove the excess metals causing oxidative damage.
Deferoxamine (DFO) Clinical Trial

• Twice daily intramuscular injections of DFO to Alzheimer’s patients over 24 months significantly reduced the rate of decline of daily living skills (p=0.03).

• The mean rate of decline was twice as rapid for the no-treatment group as compared to the DFO treated group.

• Further studies were not performed, in part due to the very short half-life of DFO in the blood.

• Intranasal DFO Targets the Brain

• Currently preparing for first in human trials of Intranasal DFO
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