How Nutrition Changes the Aging Brain

MILD COGNITIVE IMPAIRMENT AND ALZHEIMER’S DISEASE

Nafisa Jadavji, PhD
nafisa.jadavji@carleton.ca
Lecture Outline

• Topics from lecture #2
• Mild Cognitive Impairment
  • Introduction
  • Impact of Nutrition
• Questions
• Break
• Alzheimer's disease
  • Introduction
  • Impact of Nutrition
• Questions
Vitamin B12

- Deficiency leads to neurological disorders
- Memory loss
- Fatigue
- Myelopathy: disease of spinal cord
- Neuropathy: disease of the nerves
- Brain atrophy
- Neurodegenerative diseases
- Gait abnormalities
- Molecular level: development of nerve cells, myelination

Vitamin B12 in aging

- Reduced absorption as we age
- The vitamin depends on a molecule called "intrinsic factor (IF)" for absorption through the gut
- Reduced levels of IF as we age
- Oral administration or injections of vitamin B12 bypass IF
Water dehydration in elderly

% of US elderly not meeting recommendations

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-74 y</td>
<td>63%</td>
</tr>
<tr>
<td>75-84 y</td>
<td>73%</td>
</tr>
<tr>
<td>85+ y</td>
<td>81%</td>
</tr>
</tbody>
</table>

Cut-off used: 3700 ml (men) or 2700 ml (women) /day (US recommendations)

Although data on dehydration frequency in community-dwelling elderly are conflicting, comparison of their actual fluid intakes with current recommendations clearly indicates that the aging population, whether in healthcare institutions or in the community, is at risk of inadequate fluid intake, and therefore is exposed to dehydration.
Alpha-synuclein

- Abundant in the human brain
- Mostly found in neurons, presynaptic terminals
- Thought to help with neurotransmitter release
- Role not well understood

- Higher levels in PD, AD, other diseases termed synucleinopathies
Neurodegeneration

- **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
Introduction to Mild Cognitive Impairment (MCI)

• Intermediate stage between cognitive decline of normal aging and more serious decline of dementia

• Problems with memory, language, thinking and judgement greater than normal age related changes

• May increase risk of progressing to dementia to AD

• But some people with MCI do not get worse or better
What happens to the brain during MCI?

• MCI patients often but not always have:
  • Abnormal clumps of beta-amyloid protein (plaques)
  • Clumps of tau tangles
What happens to the brain during MCI?

- MCI patients often but not always have:
  - Lewy bodies, protein clumps associated with Parkinson's disease and Alzheimer's disease
What happens to the brain during MCI?

- MCI patients often but not always have:
  - Small strokes or reduced blood flow to the brain via vessels
What happens to the brain during MCI?

- Shrinkage of hippocampus (memory function)
What happens to the brain during MCI?

- Enlargement of brain’s fluid spaces (ventricles)
What happens to the brain during MCI?

- Reduced glucose, primary source of energy cells
Risk Factors for MCI

• Increasing age

• Specific form of gene known as APOE-e4, not guarantee having gene will ensure you experience cognitive decline

• Other risk factors:
  • Diabetes
  • Smoking
  • High blood pressure
  • Lack of physical exercise
  • Infrequent participation in mentally or socially stimulating activities
How is MCI assessed?

• Medical professional determines, the presences or absence of MCI by evaluating a person’s cognitive and behavioral changes

• Hallmark symptoms: forget important information, such as appointments, conversations or recent events

• Non-memory symptoms
  • Impaired thinking skills
  • E.g. trouble finding words, losing train of thought, difficulty organizing or planning
The difference from MCI and Alzheimer's disease

https://www.youtube.com/watch?v=Fm73DHzwG3M
Changes in the brain of MCI and AD

Normal                     Mild Cognitive Impairment                     Alzheimer’s disease

Figure 2. Coronal MRI Scans from Patients with Normal Cognition, Mild Cognitive Impairment, and Alzheimer’s Disease.

The arrows depict the hippocampal formations and the progressive atrophy characterizing the progression from normal cognition (Panel A) to mild cognitive impairment (Panel B) to Alzheimer’s disease (Panel C).

Petersen et al., 2011
Changes in the brain of MCI and AD

Yellow indicates amyloid deposits

Figure 3. Axial Scans of the Brain Obtained with Positron-Emission Tomography and the Use of Amyloid-Binding Carbon 11–Labeled Pittsburgh Compound B.

The yellow and red areas indicate retention of the amyloid-binding tracer, reflecting amyloid deposits. The patient with normal cognition (Panel A) has no tracer retention, whereas the patient with amnestic mild cognitive impairment has an intermediate amount of tracer retention (Panel B) and the patient with Alzheimer’s disease has prominent tracer retention (Panel C).

Petersen et al., 2011
Vitamin E Introduction

• Antioxidant
• Studies show protectiveness in CNS against oxidative stress
• Essential for central nervous system
• Protects cell membranes
Vitamin E and neurological function

Normal membrane

Lipid peroxidation

Integral protein

Peripheral protein

Protein damage

Membrane damage

DNA damage

Mitochondrial damage

Nucleus

Inside

Outside

$\text{OH}^-$

$10^{-19}$ M

$\text{Ca}^{2+}$

$\text{Na}^+$

$\text{H}_2\text{O}$

Changes in membrane permeability
Vitamin MCI Study

- 2000 IU of vitamin E daily
- 3 years
- Found no benefits of vitamin E for Mild Cognitive Impairment

Peterson et al., 2005
Malnutrition & MCI

• 100 men and women in elderly homes in Cairo, Egypt

• 38 individuals had MCI

• Older adult with MCI had higher risk of being malnourished

• Importance of identifying nutritional status with MCI

Khaler, 2011
B-vitamin: Folates

- Obtained from diet
Folate: natural form
Folic Acid
Homocysteine

• Molecule, amino acid

• High levels associated with:
  • Cardiovascular disease, changes blood vessels
  • Pregnancy complications: Neural tube defects
  • Neurodegeneration (Lecture 3)
Folate and Homocysteine

• Folates reduce levels of homocysteine

• More folate in the body, reduced homocysteine levels

• Less folate in the body higher levels of homocysteine

• Other factors also affect levels of homocysteine, such as medication, coffee intake and alcohol consumption
Folate supplementation in Elderly

Study Background
- 2004-06
- Patients with Mild Cognitive Impairment (MCI) & controls
- Treatment, 2 years; Folic Acid and Vitamin B12

Smith et al., 2010
Folate supplementation in Elderly
Folate supplementation in Elderly

Placebo

Treated
Effect of B-vitamin supplementation on grey matter volume in patients with Mild Cognitive Impairment

**Objective**: investigate whether Alzheimer's disease related gray matter atrophy can be reduced via B-vitamin supplementation

- Patients: Mild Cognitive Impairment
- 2 Years of B-vitamin supplementation
- MRI
Results

B-vitamin supplementation for 2 years reduces brain shrinkages by 7-fold
**Results**

Treated individuals with the highest levels of homocysteine benefited most from B-vitamin supplementation.
Grain Fortification Legislation

84 countries require fortification of wheat flour, maize flour, and/or rice

August 2015. Source: Food Fortification Initiative.
To request data, e-mail info@ffinetwork.org
Questions?
BREAK!
Alzheimer’s disease overview

INCREASED LEVELS OF:
- amyloid beta protein
- tau
Risk factor of Alzheimer’s disease

• Increase with age
• Doubles every 5 years after 65
  • Changes occur over time → additive
  • 100 million worldwide by 2050
What is Alzheimer’s disease?

- Neuronal loss
- Synaptic dysfunction
- Gliosis
- Increased levels of tau (protein)
- Plaques
- Amyloid beta protein fibrillary aggregates
Alzheimer’s disease

2 major hypotheses:
- Increase in tau
- Amyloid beta aggregation
Diabetes and Alzheimer’s disease

• Risk of diabetes increase with age
• Diabetes and AD interrelated
• Diabetes a major risk factor for AD

• Studies show glucose intolerance and impaired insulin secretion are risk factors for dementia
Diabetes and Alzheimer’s disease

• Obesity predispose individuals to type 2 diabetes linked to cognitive impairment and development of AD

• Bariatric surgery weight loss improved cognition

• Caloric restriction helps minimize effect of aging
Diabetes and Alzheimer’s disease

• Number of diabetes drugs such as insulin effective in treating AD in mouse models

• Triple receptor agonist

Comparison between agonist & antagonist:
Diabetes and Alzheimer’s disease

• APP/PS1 mice whose brains were in the advanced stages of degeneration.

• APP/PS1 mice are engineered "transgenic mice" that carry versions of human genes that are linked to an inherited form of Alzheimer’s.
Diabetes and Alzheimer’s disease

- Drug: activates the proteins that allow signals from three growth factors — called glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, and glucagon

- In a maze learning test, the treated mice showed improved memory formation.

- Brain tissue showed a reduction in
  - amyloid plaques
  - inflammation
  - oxidative stress

Recent study: January 2018
Folic Acid: Clinical study

• Study published in 2002
• 1092 subjects without dementia (667 women and 425 men, ~76 years old)
• Followed for 8 years
• Increased levels of plasma homocysteine risk factor for dementia and Alzheimer’s disease

Clinical studies looking at homocysteine levels in patients with Alzheimer's disease

- Study published in 2005
- 145 patients with AD
- High homocysteine levels and plasma levels of amyloid beta protein were correlated

Reference: NEUROLOGY 2005;65:1402–1408
Clinical studies looking at homocysteine levels in patients with Alzheimer's disease
Clinical study investigating memory and homocysteine levels

• Study published in 2011
• Conducted in US
• 228 individuals (ages 80-101)
• Found no association between homocysteine levels and memory

Am J Geriatr Psychiatry 19:7, July 2011
Mediterranean diet and Alzheimer’s disease

• Mediterranean diet related to lower risk for cardiovascular disease
• Study: 2258 individuals, no dementia
• Maintained on Mediterranean diet, adherence was evaluated

• 4 years, 262 developed Alzheimer’s disease
• Found higher adherence to Mediterranean diet associated with lower risk for Alzheimer’s disease

Sandman et al., 2006
Overview of nutrition status & neurodegeneration

Kamphusia et al., 2010
Neurodegeneration

• Changes in brains of persons at risk for developing AD
  • Develop 20-30 year prior to dementia symptoms

• Early nutrition supplements can be initiated with greater potential

• Further along in disease process, supplementation of specific brain supportive nutrient may still prevent deterioration or improve brain function

Kamphusia et al., 2010
The impact of diet on Alzheimer's disease

FIGURE 1: Foods and beverages that influence the incidence of AD. Fish, vegetables, fruits, coffee, and light-to-moderate alcohol intake are reported to reduce AD incidence. Milk and tea are reported to influence cognition, but their influence on AD is not clear.

Hu et al., 2013
The impact of diet on Alzheimer's disease

- Antioxidants: decrease oxidative stress, antioxidants in prevention of AD

- Vitamin E: fat soluble antioxidant, neuroprotective by inhibiting oxidative stress and scavenging amyloid beta associated free radicals

Hu et al., 2013
The impact of diet on Alzheimer's disease

• Zinc: supplementation reported to reduce amyloid beta and tau pathologies deficiency is reported to be associated with cognition loss in AD patients

• Vitamin D: supplementation could prevent cognitive decline

Hu et al., 2013
Phytochemicals

- Plant derived chemical compounds
- Have health prompting properties (e.g. green tea, curcumin)
- Basic science research has shown positive effects
- Unwise to extrapolate these results to the human situation without a proper clinical trial
Phytochemicals

• Animal models, no extensive neuronal lost

• Short-tern basis of animals and in vitro studies, human diseases are more long term

• No clinical trials conducted
Alzheimer's disease and cholesterol

• AD caused by deficiency of cholesterol, fats, and oxidative stress

• Diet:
  • High in carbohydrates (high glycemic index), e.g. fructose
  • Low in fats and cholesterol

*fructose is a sweeting agent, that is 10X as reactive as glucose

Leads to destructive process and begins with glycation damage and synthesis of cholesterol
Alzheimer's disease and cholesterol

- Amyloid beta synthesis is a protective mechanism
- It redirects metabolism away from glucose, mitochondria, and decrease in oxidative damage and damage from glycation
- Cerebrospinal fluid in AD patients is deficient in fats and cholesterol
- Synthesis of glutamate is increased when cholesterol is deficient
Cholesterol and AD

https://www.youtube.com/watch?v=HtpvsT5vGCg
Lecture Summary

• Neurodegeneration is a progressive loss of function

• There are some nutritional benefits to combat mild cognitive impairment and Alzheimer's disease

• Nutrition and neurodegeneration is complex interaction
Next week....Vascular Dementia & Dietary Influences on Cognition in Aging
Questions?