LATEST DIAGNOSIS AND TREATMENT

Serge Gauthier, C.M., MD, FRCPC
McGill University Research Center for Studies in Aging
Douglas Mental Health University Institute
Montréal, Canada
OUTLINE

• What is Alzheimer’s disease?
• What is new in the diagnosis?
• What is new in the treatment?
• What is coming next?
WHAT IS ALZHEIMER’S DISEASE?

A progressive neurodegenerative disease affecting initially the temporal areas of the brain [memory], then posterior associative areas [language, spatial orientation], then frontal lobes [personality & behavior]
[18F]FDG of normal vs AD
WHAT IS ALZHEIMER’S DISEASE?

PATHOLOGY

• Classic pathology includes amyloid plaques and neurofibrillary tangles
• Most patients also have small strokes
• Many patients also have Lewy Bodies
PATHOLOGIES ASSOCIATED WITH AD

AGE

30  β-amyloid Deposition (plaques)
40  Microglial Activation (inflammation)
50  NFTs (tangles)
60  Neuronal Loss (atrophy)
70  
80  
90  
100  Symptoms
WHAT IS ALZHEIMER’S DISEASE?

BIOMARKERS

• “Pathophysiology markers” include amyloid deposition seen on PET scans and lower CSF levels of β42

• “Neurodegeneration markers” include brain atrophy on MRI, hypometabolism on PET-FDG, higher CSF levels of phospho-tau
AMYLOID PET IN MUTATION CARRIERS

15 years prior to estimated symptoms
10 Years prior to estimated symptoms
~5 years after Alzheimer’s disease

Courtesy of Mark Mintun and Randy Bateman
AD PROGRESSION USING BIOMARKERS

Relationship between “abnormality” and CDR of 1.0


- Aβ deposition
- Hippocampal volume
- Episodic memory
- Grey matter volume
- Non-memory

Biomarker magnitude

Time (years)

CDR 1.0

abnormal

normal

non-demented
demented

Cut-off
WHAT IS ALZHEIMER’S DISEASE?

GENETIC FACTORS

• Autosomal dominant early onset (<65) infrequent but important as involving only amyloid mutations (PS1, PS2, APP)

• ApoE4 genotype frequent (15%) and is the major genetic risk factor in late-onset AD

• Genes effects can be additive or protective (for example the HMGCR’s G negative allele)
Mild Cognitive Impairment (MCI) Conversion to AD by ApoE Status

Probability of not converting to AD

Apoe4 negative
Apoe4 positive
Apoe4 positive – HMGR G-Negative

Time on MCI study (days)

N= 769 Subjects
NEJM June 2005
WHAT IS ALZHEIMER’S DISEASE?
RISK AND PROTECTIVE FACTORS

RISK FACTORS

- Alcohol misuse
- Hypertension
- Obesity
- Dyslipidemia
- Diabetes
- Vascular insults
- Neuronal damage

PROTECTIVE FACTORS

- APOE, Other genes
- Unhealthy diet
- Smoking
- Physical activity
- Cognitive and social activity
- Education
- Brain reserve

WHAT IS ALZHEIMER’S DISEASE?
RISK AND PROTECTIVE FACTORS

Mangialasche, Kivipelto et al., 2012
OUTLINE

• What is Alzheimer’s disease?
• **What is new in the diagnosis?**
• What is new in the treatment?
• What is coming next?
WHAT IS NEW IN THE DIAGNOSIS?

- Validation of new diagnostic criteria proposed by the IWG and the NIA-AA workgroups.
- There has to be a balance between sensitivity, specificity and affordability.
- Sharing of data from large observational studies (ADNI, AIBL, new CCNA).
WHAT IS NEW IN THE DIAGNOSIS?

• Interest in ‘asymptomatic AD’ for preventive studies, e.g. biomarker or ApoE4 positivity and no symptoms

• Ethical issues in disclosing results of biomarkers and genetic testing for is a “risk state”, not a clinical disease

• Special case of mutations causing familial early onset AD
OUTLINE

• What is Alzheimer’s disease?
• What is new in the diagnosis?
• What is new in the treatment?
• What is coming next?
## MODIFYABLE RISK FACTORS

(Barnes and Yaffe, 2011)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Population Prevalence</th>
<th>Relative Risk (95% CI)</th>
<th>PAR (confidence range)</th>
<th>Number of Cases Attributable (thousands; confidence range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worldwide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6.4%</td>
<td>1.39 (1.17-1.66)</td>
<td>2.4% (1.1-4.1)</td>
<td>826 (365-1374)</td>
</tr>
<tr>
<td>Midlife hypertension</td>
<td>8.9%</td>
<td>1.61 (1.16-2.24)</td>
<td>5.1% (1.4-9.9)</td>
<td>1746 (476-3369)</td>
</tr>
<tr>
<td>Midlife obesity</td>
<td>3.4%</td>
<td>1.60 (1.34-1.92)</td>
<td>2.0% (1.1-3.0)</td>
<td>678 (387-1028)</td>
</tr>
<tr>
<td>Depression</td>
<td>13.2%</td>
<td>1.90 (1.55-2.33)</td>
<td>10.6% (6.8-14.9)</td>
<td>3600 (2295-5063)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>17.7%</td>
<td>1.82 (1.19-2.78)</td>
<td>12.7% (3.3-24.0)</td>
<td>4297 (1103-8122)</td>
</tr>
<tr>
<td>Smoking</td>
<td>27.4%</td>
<td>1.59 (1.15-2.20)</td>
<td>13.9% (3.9-24.7)</td>
<td>4718 (1338-8388)</td>
</tr>
<tr>
<td>Low education</td>
<td>40.0%</td>
<td>1.59 (1.35-1.86)</td>
<td>19.1% (12.3-25.6)</td>
<td>6473 (4163-8677)</td>
</tr>
<tr>
<td>Combined (maximum)</td>
<td>--</td>
<td>--</td>
<td>50.7%</td>
<td>17187 028*</td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8.7%</td>
<td>1.39 (1.17-1.66)</td>
<td>3.3% (1.5-5.4)</td>
<td>174 (77-288)</td>
</tr>
<tr>
<td>Midlife hypertension</td>
<td>14.3%</td>
<td>1.61 (1.16-2.24)</td>
<td>8.0% (2.2-15.1)</td>
<td>425 (119-798)</td>
</tr>
<tr>
<td>Midlife obesity</td>
<td>13.1%</td>
<td>1.60 (1.34-1.92)</td>
<td>7.3% (4.3-10.8)</td>
<td>386 (226-570)</td>
</tr>
<tr>
<td>Depression</td>
<td>19.2%</td>
<td>1.90 (1.55-2.33)</td>
<td>14.7% (9.6-20.3)</td>
<td>781 (506-1078)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>32.5%</td>
<td>1.82 (1.19-2.78)</td>
<td>21.0% (5.8-36.6)</td>
<td>1115 (308-1942)</td>
</tr>
<tr>
<td>Smoking</td>
<td>20.6%</td>
<td>1.59 (1.15-2.20)</td>
<td>10.8% (3.0-19.8)</td>
<td>574 (159-1050)</td>
</tr>
<tr>
<td>Low education</td>
<td>13.3%</td>
<td>1.59 (1.35-1.86)</td>
<td>7.3% (4.4-10.3)</td>
<td>386 (236-544)</td>
</tr>
<tr>
<td>Combined (maximum)</td>
<td>--</td>
<td>--</td>
<td>54.1%</td>
<td>2866 951*</td>
</tr>
</tbody>
</table>

PAR = population attributable risk. * Absolute number.

Table: Alzheimer's disease cases attributable to potentially modifiable risk factors worldwide and in the USA
WHAT IS NEW IN TREATMENT?
NON-PHARMACOLOGIC STUDIES

• FINGER
<table>
<thead>
<tr>
<th>CAIDE Dementia Risk Score</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 47 years</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>47-53 years</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt;53 years</td>
<td>4</td>
</tr>
<tr>
<td>Formal education</td>
<td>≥10 years</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>7-9 years</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0-6 years</td>
<td>3</td>
</tr>
<tr>
<td>Gender</td>
<td>Women</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>1</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>≤ 140 mm Hg</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 140 mm Hg</td>
<td>2</td>
</tr>
<tr>
<td>BMI</td>
<td>≤ 30 kg/m²</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 30 kg/m²</td>
<td>2</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>≤ 6.5 mmol/l</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 6.5 mmol/l</td>
<td>2</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Active</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Inactive</td>
<td>1</td>
</tr>
</tbody>
</table>

Kivipelto et al., Lancet Neurol 2006
INCLUSION CRITERIA: persons at risk of dementia/cognitive decline

- Dementia Risk score $\geq$ 6 points
  
  Based on risk factors assessed in earlier population surveys: Age, Education, Sex, SBP, Cholesterol, BMI, Physical Activity (Kivipelto et al., Lancet Neurology 2006)

AND

- Cognitive performance at mean level or slightly lower than expected for age
  
  (based on CERAD test battery)

Protocol in Kivipelto et al., Alzheimer & Dementia 2013
INTERVENTION SCHEDULE

INTENSIVE MULTIDOMAIN INTERVENTION

NUTRITION:
7 group sessions,
3 individual sessions

EXERCISE:
1-2x/wk muscle
2-4x/wk aerobic
EXERCISE:
2x/wk muscle
4-5x/wk aerobic
EXERCISE:
2x/wk muscle strength training
5-6x/wk aerobic training

COGNITIVE TRAINING:
9 group sessions
Independent training
COGNITIVE TRAINING:
2 group sessions
Independent training

MONITORING AND MANAGEMENT OF
METABOLIC AND VASCULAR RISK FACTORS
Nurse: Visit every 3 months, Physician: 3 additional visits

REGULAR HEALTH ADVICE

Kivipelto et al., Alzheimer & Dementia 2013
Primary efficacy outcome: overall cognition (NTB composite Z score)

Difference between intervention and control groups per year:
Estimate (95% CI) = 0.022 (0.002-0.042)
p=0.03

Lines = estimates for cognitive change from baseline to 12 and 24 months
Higher scores = better performance
Error bars = standard errors.
P-values = difference in trajectories over time between groups

Kivipelto et al, Lancet 2015
Intervention effects on main cognitive secondary outcomes

Difference between intervention and control groups per year:
Estimate (95% CI), p-value

0.027 (0.001-0.052)  p=0.04
0.030 (0.003-0.057)  p=0.03
0.015 (-0.017-0.048) p=0.36

Kivipelto et al, Lancet 2015
WHAT IS NEW IN TREATMENT?
PHARmacologic Studies

• ADUCANUMAB
β-Amyloid treatment strategies under study

APP gene

Production

APP

Antisense

Secretase inhibitors & modulators

Aβ Monomer

Aβ Oligomer

Aggregation

Aβ Fibril

Fibrillogenesis modulators

Deposition

Diffuse Plaque

Senile Plaque

Immunotherapy

Anti-inflammatory
Aducanumab Background

- Human monoclonal antibody selective for aggregated forms of beta-amyloid, including soluble oligomers and insoluble fibrils

- In Tg2576 mouse model of AD:
  - Dose-dependent reduction of Aβ with chronic dosing
  - Microglia-mediated phagocytosis of amyloid plaques

- A single ascending dose study\(^2\) of aducanumab demonstrated acceptable safety and tolerability in mild-to-moderate AD subjects at doses up to 30 mg/kg


Aducanumab is an investigational drug and not approved in Canada
Amyloid Plaque Reduction with Aducanumab

Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.

Aducanumab is an investigational drug and not approved in Canada.
Aducanumab Effect on CDR-sb

CDR-sb is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-sb. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

Aducanumab is an investigational drug and not approved in Canada.
OUTLINE

• What is Alzheimer’s disease?
• What is new in the diagnosis?
• What is new in the treatment?
• What is coming next?
WHAT IS COMING NEXT?

• Learn from observations in people with recurrent head injuries, Down’s syndrome
• Share “big” data, e.g. pool information from around the world
• PET-tau brain scanning may be closer to the pathology causing symptoms
• Learn from the protective genes
• National policies to support education and maintain healthy life-styles