IMPACT OF NEW TECHNOLOGY TOWARDS RISK ASSESSMENT FOR AD: METHODS, CRITERIA, RISKS AND BENEFITS

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Disclosures

Member of advisory board, DSMB, speaker or investigator with:

AbbVie, Affiris, Eisai, Ever, GE Health Care, Lundbeck, Lilly, Merck, Merz, Novartis, Pfizer, Sanofi-Aventis, Servier, TauRx
OUTLINE

- Risk for developing AD
- Prevention studies
- Ethical issues
Life-course approach in dementia/AD risk

Risk Factors
- Unhealthy diet
- Alcohol misuse
- Smoking
- Obesity
- Hypertension
- Hypercholesterolemia
- Diabetes
- Vascular insults
- Neuronal damage
- Brain reserve
- APOE
- Other genes

Protective Factors
- Adult life
- Middle age
- Transition
- Old age
- Education
- Physical activity
- Mental and Social activity

0 20 60 75
<table>
<thead>
<tr>
<th>CAIDE Dementia Risk Score</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>&lt; 47 years 47-53 years &gt;53 years</td>
<td>034</td>
</tr>
<tr>
<td><strong>Formal education</strong></td>
<td>≥10 years 7-9 years 0-6 years</td>
<td>023</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Women  Men</td>
<td>01</td>
</tr>
<tr>
<td><strong>Systolic BP</strong></td>
<td>≤ 140 mm Hg &gt; 140 mm Hg</td>
<td>02</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>≤ 30 kg/m2 &gt; 30 kg/m2</td>
<td>02</td>
</tr>
<tr>
<td><strong>Total cholesterol</strong></td>
<td>≤ 6.5 mmol/l &gt; 6.5 mmol/l</td>
<td>02</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td>Active  Inactive</td>
<td>01</td>
</tr>
</tbody>
</table>

Kivipelto et al., Lancet Neurol 2006
### Probability of dementia in late-life according to the Dementia Risk Score category in middle age

The overall occurrence of dementia 4.4%

<table>
<thead>
<tr>
<th>SCORE</th>
<th>All /Demented, n</th>
<th>% Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>401 / 4</td>
<td>1.0 (0.0-2.0)</td>
</tr>
<tr>
<td>6-7</td>
<td>270 / 5</td>
<td>1.9 (0.2-3.5)</td>
</tr>
<tr>
<td>8-9</td>
<td>312 / 13</td>
<td>4.2 (1.9-6.4)</td>
</tr>
<tr>
<td>10-11</td>
<td>245 / 18</td>
<td>7.4 (4.1-10.6)</td>
</tr>
<tr>
<td>12-15</td>
<td>122 / 20</td>
<td>16.4 (9.7-23.1)</td>
</tr>
</tbody>
</table>
PATHOLOGIES ASSOCIATED WITH AD

AGE

30  β-amyloid deposition
40  Microglial activation
50  NFTs
60  Neuronal loss
70  
80  
90  
100  Symptoms
BIOMARKERS FOR AD

* Amyloid build up
  - PET amyloid (high)
  - CSF Aβ42 (low)

* Evidence of neuronal injury
  - CSF tau (high)
  - MRI (atrophy)
  - PET-FDG (hypometabolism)
## SPINAL FLUID (CSF) IN AD

<table>
<thead>
<tr>
<th></th>
<th>Aβ42</th>
<th>Tau</th>
<th>Ptau</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD</strong></td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>MCI</strong></td>
<td>↓ or N</td>
<td>↑ or N</td>
<td>↑ or N</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

- **Aβ42**: in senile plaques
- **Phosphorylated tau (Ptau)**: in neuronal axons
- **Total tau** in neuronal axons

**Abbreviations**
- AD: Alzheimer's Disease
- MCI: Mild Cognitive Impairment
- Cont: Control

**Notes**
- AD patients have decreased Aβ42 and increased Tau and Ptau.
- MCI patients show a decrease or normal levels of Aβ42, with increased Tau and Ptau.
- Control individuals have normal levels of Aβ42, Tau, and Ptau.

**Visual Elements**
- Neuronal diagram illustrating Aβ1-42 in senile plaques and phosphorylated tau in neuronal axons.
MRI IN AD

Rated area
[18F]FDG of normal vs AD
Alzheimer’s disease exists on a spectrum from minimal symptoms to dementia

- No symptoms
- Mild cognitive symptoms
- Dementia

- Increasingly severe phenotype
- Biomarkers assist in identifying the underlying pathology
- Biomarker changes may precede clinically detectable changes

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AD PROGRESSION USING BIOMARKERS

Abnormal

- CSF Aβ42
- Amyloid imaging
- FDG-PET
- MRI hippocampal volume
- CSF Tau
- Cognitive performance
- Function (ADL)

Normal

Presymptomatic eMCI LMCI Dementia

FDG-PET MRI hippocampal volume
CSF Aβ42
Amyloid imaging
Cognitive performance
Function (ADL)
CSF Tau

DIAGNOSTIC CRITERIA FOR PRECLINICAL AD USING BIOMARKERS
(Modified from Sperling et al, 2011)

- Asymptomatic cerebral amyloidosis (ACA) + - -
- ACA + evidence of neuronal injury (NI) + + -
- ACA + NI + subtle cognitive decline + + +
RISKS FOR DEVELOPING AD

- Dementia Risk Score, mid-life (predominantly vascular risk factors)
- Genetics (ApoE4)
- Amyloid build-up in the brain (PET)
OUTLINE

- Risk for developing AD
- Prevention studies
- Ethical issues
Survival design from CN to DEMENTIA

% persons without dementia

Time (years)

Disease modifying Rx

Placebo
INCIDENT DEMENTIA IN FRENCH GINKGO STUDY

Figure FPH-14.2.1.5: Conversion to Pure Alzheimer Type Dementia - Kaplan-Meier Plot for Median Time to Conversion
ITT Population

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>EGb 761 120mg</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
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<tr>
<td>12</td>
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<tr>
<td>24</td>
<td></td>
<td></td>
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<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td></td>
<td></td>
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<td>54</td>
<td></td>
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<tr>
<td>60</td>
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</tbody>
</table>

Number of subjects at risk:

- EGb: 1406, 1129, 1022, 944, 865, 29
- Placebo: 1414, 1128, 1048, 966, 874, 20

Number of subjects with Alzheimer's disease diagnosis:

- EGb:
  - 22, 15, 8, 6, 10
- Placebo:
  - 21, 11, 11, 12, 18
PREVENTION STUDIES IN ASYMPTOMATIC AT RISK PERSONS – no drugs

- High Dementia Risk Score (FINGER, multidomain interventions with cognitive training, physical exercises, better diet, control of vascular risk factors)

LOW RISK FOR DISEASE vs
LOW RISK TREATMENT
PREVENTION STUDIES IN ASYMPTOMATIC AT RISK PERSONS – non-Aβ drugs

- Family history late onset (Stop-AD: naproxen, probuchol; Zinfandel-Takeda, pioglitazone)

MODERATE RISK FOR DISEASE vs SLIGHTLY HIGHER RISK TREATMENT
PREVENTION STUDIES IN ASYMPTOMATIC AT RISK PERSONS – Aβ immunotherapy

- Family history for early onset AD, mutation carriers (DIAN-TU, API)
- Amyloid in brain (A4)
- A4/4 (API)

HIGHER RISK FOR DISEASE vs HIGHER RISK TREATMENT
Anti-amyloid immunotherapy: What Can Go Wrong?

- CD3 T-cell meningeal response to AN-1792
- Vasculitis
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Intra-cerebral Microhemorrhage
- Accelerated Brain Atrophy
PREVENTION STUDIES

- There are a number of prevention studies that took place and others ongoing
- The inclusion criteria take into account the risk of developing AD
- Some of the treatments have risks
OUTLINE

- Risk for developing AD
- Prevention studies
- Ethical issues
DISCLOSURE OF RISK

- The simple fact that you are accepted in a prevention study means that you are at higher risk
  - Dementia Risk Score
  - Genetic tests
  - Amyloid scan
RISKS OF AD vs RISKS OF TREATMENT

- The risks should be balanced
Figure 1: Conceptual framework anticipating AD prevention trials. Large samples (Boxes A, B, and C) are differentiated on the basis of genetic risk. The overlap between the three boxes is for heuristic purposes only and is not meant to imply any precise degree of risk. Groups within each box are differentiated by the presence of clinical symptoms (blue for asymptomatic and orange for symptomatic). Stratification illustrates individual status as positive or negative for biomarkers (BioM). The lower portion of the figure illustrates the degree of risk for dementia for the samples and groups. Superimposed on the framework are therapeutic risk-benefit ratios as a function of risk category.
CONCLUSIONS

- The risk for developing AD can be quantified in simple or in complex ways.
- Prevention studies are ongoing and take into account those risks.
- Ethical issues are important since participants have no symptoms, the risk prediction towards AD is uncertain, and there are risks associated with some of the treatments.