Vascular Risk Factors in Alzheimer’s Disease

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Connection between vascular disease and dementia

Hypertension or VRF, CV disease

Stroke ↔ SVD

Vascular cognitive impairment

Dementia; vascular or Alzheimer

β-amyloid

Neurodegenerative brain lesion
Age-related frequency of neuropathologic types of dementia

Shared risk factors for AD and CVD

- **Framingham Cardiovascular Risk Profile (FCRP)**
  - age, gender, diabetes, smoking, treated and untreated systolic BP, total cholesterol (TC), and HDL

- **Framingham Stroke Risk Profile (FSRP)**
  - age, systolic blood pressure, history of diabetes, current cigarette smoking, prevalent cardiovascular disease, history of atrial fibrillation, and left ventricular hypertrophy

- **Cardiovascular Risk Factors Aging and Dementia (CAIDE) risk score**
  - age, educational level, hypertension, hypercholesterolemia, obesity, and physical inactivity
High FSRP scores are associated with worsening of cognitive abilities

- 3,117 MCI (74±8 years, 56% female) and 6,603 NC participants (72±8 years, 68% female) were drawn from the National Alzheimer’s Coordinating Center.
- In NC participants
  - increasing FSRP was related to worse baseline global cognition, information processing speed, and sequencing abilities (p < 0.0001) and a worse longitudinal trajectory on all cognitive measures (p < 0.0001).
- In MCI
  - increasing FSRP correlated with worse longitudinal delayed memory (p = 0.004).

CAIDE Risk score for the prediction of dementia risk in 20 years

<table>
<thead>
<tr>
<th></th>
<th>Low risk profile</th>
<th>Intermediate risk profile</th>
<th>High risk profile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1 score=0</td>
<td>Model 2 score=0</td>
<td>Model 1 score=15</td>
</tr>
<tr>
<td></td>
<td>Model 2 score=0</td>
<td>Model 2 score=10</td>
<td>Model 2 score=18</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;47 years</td>
<td>47-53 years</td>
<td>&gt;53 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Education</td>
<td>≥10 years</td>
<td>7-9 years</td>
<td>≤6 years</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>≤140 mm Hg</td>
<td>&gt;140 mm Hg</td>
<td>&gt;140 mmHg</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>≤30 kg/m²</td>
<td>≤30 kg/m²</td>
<td>&gt;30 kg/m²</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>≤6-5 mmol/L</td>
<td>&gt;6-5 mmol/L</td>
<td>&gt;6-5 mmol/L</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Active</td>
<td>Inactive</td>
<td>Inactive</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>..</td>
<td>Non ε4</td>
<td>ε4</td>
</tr>
<tr>
<td>Risk of dementia</td>
<td>0.13%</td>
<td>6.91%</td>
<td>35.55%</td>
</tr>
<tr>
<td></td>
<td>0.09%</td>
<td>4.06%</td>
<td>48.93%</td>
</tr>
</tbody>
</table>

The dementia risk score was modelled as a continuous variable and the parameters of the model were used to assess the risk level related to specific scores.

*Table 4: Risk of dementia for low, intermediate, and high-risk individuals, according to the dementia risk score in the CAIDE population*
CAIDE Risk score for the prediction of dementia risk in 20 years

Figure: Receiver-operating characteristic curves showing the performance of the dementia risk scores in predicting the risk of dementia in 20 years among those in middle age.

The AUC for model 1 was 0.769 (95% CI 0.709–0.829). The AUC for model 2 was 0.776 (0.717–0.836).

Lancet Neurol. 2006 Sep;5(9):735-41
CAIDE risk score for the prediction of dementia 40 years later

Step 1
- Age, y
  - 40–46: 0 points
  - 47–53: 3 points
  - 54–55: 4 points

Step 2
- Education, y
  - 0–6: 3 points
  - 7–9: 2 points
  - >9: 0 points

Step 3
- Sex
  - Men: 1 point
  - Female: 0 points

Step 4
- Cholesterol, mg/dL
  - <251: 0 points
  - ≥251: 2 points

Step 5
- BMI, kg/m²
  - <30: 0 points
  - ≥30: 2 points

Step 6
- Systolic blood pressure, mm/Hg
  - <140: 0 points
  - >140: 2 points

Predicted 40-year risk of dementia

Add up points from steps 1 through 6, then look up predicted 40-year risk of dementia.

Alzheimers Dement. 2014 Sep;10(5):562-70
Previous reports about AD progression

- **Relationship of vascular risk to the progression of Alzheimer disease.**
  - There was no difference in rate of deterioration between people with and without vascular risk factors, except in those who had a **CVA** during the 18-month follow-up.

- **Vascular factors predict rate of progression in Alzheimer disease.**
  - Atrial fibrillation, hypertension, and angina were associated with a greater rate of decline during the 3-year follow-up.

- **Contribution of vascular risk factors to the progression in Alzheimer disease.**
  - Higher prediagnosis total cholesterol and LDL-C concentrations and history of diabetes were associated with faster cognitive decline.

FCRP can predict cognitive decline progression in AD

CDR score from 1 to 2/3 from baseline to the 12-month evaluation

Framingham Risk Score (Overall Population)

AUC=0.63

N=284

Framingham Risk Score (ApoE4 carriers)

AUC=0.71

Shared pathophysiology?

• A link between cardiovascular disease and AD-specific biomarkers?
• A link between cardiovascular disease and AD-specific pathology?
  – Amyloid
  – Tau
  – Neurodegeneration
Associations of CAIDE Risk Score with MRI, PIB-PET measures, and cognition

**FINRISK cross-sectional surveys (1972-2007, every 5th year)**
Random samples (National Population Register, several regions in Finland)
Surveys of risk factors for chronic, non-communicable diseases

**FIN-D2D cross-sectional surveys (2004 & 2007)**
Random samples (National Population Register, FIN-D2D diabetes prevention project regions)
Surveys of risk factors for diabetes

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**CAIDE Dementia Risk Score**

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**Follow-up**

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**Screened for FINGER trial eligibility (2009-2011)**
N=2654

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**FINGER baseline visit**
N=1260

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**MRI scans** N=132
**PIB-PET scans** N=48
**Cognitive testing** N=1260

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**Brain MRI/PET scans (selected sites only):**
- Most recently recruited individuals at the time when MRI/PET resources became available at a specific site, and with no contraindications.
- Baseline MRI scans N=155; after quality control 23 scans were excluded (acquisition issues N=18; old infarcts N=5)
Associations of CAIDE Risk Score with MRI, PIB-PET measures, and cognition

The CAIDE Risk Score was related to indicators of cerebrovascular changes and neurodegeneration on MRI, and cognition, but lack of association with brain amyloid accumulation

J Alzheimers Dis. 2017;59(2):695-705

<table>
<thead>
<tr>
<th>CAIDE Dementia Risk Score</th>
<th>CAIDE Dementia Risk Score including APOE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>More pronounced deep WML</td>
<td>130</td>
</tr>
<tr>
<td>More pronounced periventricular WML</td>
<td>130</td>
</tr>
<tr>
<td>More pronounced MTA</td>
<td>131</td>
</tr>
<tr>
<td>Amyloid positivity on PIB-PET</td>
<td>48</td>
</tr>
<tr>
<td><em>Standardized β-coefficient (p-value)</em></td>
<td></td>
</tr>
<tr>
<td>Hippocampal volume</td>
<td>131</td>
</tr>
<tr>
<td>AD signature thickness</td>
<td>131</td>
</tr>
<tr>
<td>Total GM volume</td>
<td>131</td>
</tr>
</tbody>
</table>
CAIDE Risk Score, Alzheimer and cerebrovascular pathology: a population-based autopsy study

- Explore the relationship between CAIDE Risk Score at baseline and neuritic plaques, neurofibrillary tangles, cerebral infarcts and cerebral amyloid angiopathy (CAA) after up to 10-year follow-up in the Vantaa 85+ population (Finland)

- Study population included 149 participants aged ≥85 years, without dementia at baseline, and with available clinical and autopsy data

In a population of elderly aged ≥85 years, higher CAIDE Dementia Risk Score was associated with increased risk of cerebral infarcts.

No associations were found with other neuropathologies.

Table 2: Association of CAIDE Dementia Risk Score with neuropathology (OR, 95% CI)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Continuous</th>
<th>Dichotomous (cut-off &gt; 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tangle count</td>
<td>1.03 (0.88–1.21)</td>
<td>0.64 (0.34–1.22)</td>
</tr>
<tr>
<td>Braak stage</td>
<td>1.15 (0.98–1.34)</td>
<td>0.92 (0.50–1.68)</td>
</tr>
<tr>
<td>Amyloid-β load</td>
<td>1.13 (0.97–1.33)</td>
<td>1.01 (0.54–1.87)</td>
</tr>
<tr>
<td>CERAD score</td>
<td>1.12 (0.95–1.33)</td>
<td>0.96 (0.49–1.87)</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy</td>
<td>1.06 (0.90–1.24)</td>
<td>0.77 (0.31–1.46)</td>
</tr>
<tr>
<td>Cerebral macroinfarcts</td>
<td>1.11 (0.94–1.32)</td>
<td>1.62 (0.82–3.21)</td>
</tr>
<tr>
<td>Cerebral microinfarcts</td>
<td>1.21 (0.96–1.53)</td>
<td>2.01 (0.76–5.59)</td>
</tr>
<tr>
<td>All cerebral infarcts</td>
<td>1.17 (0.98–1.40)</td>
<td><strong>2.10 (1.06–4.16)</strong></td>
</tr>
<tr>
<td>α-synuclein pathology</td>
<td>1.05 (0.87–1.27)</td>
<td>0.76 (0.35–1.66)</td>
</tr>
</tbody>
</table>

Host factors:
- Age
- Education
- Genetics
- Vascular risk factors
- ApoE ε4
- Diabetes

Vascular causes:
- Atherosclerosis
- Microvascular diseases
- Reduced CBF
- Endothelial disorders
- Oxidative stress
- BBB dysfunction

Cerebral microinfarcts
- Lacunar state
- White matter lesions

Multiple microinfarcts

Neuronal, synapse loss

Cerebral atrophy

Additional pathologies
- Amyloid deposition
- CAA
- Aging

Cognitive impairment
- Dementia
Conclusion

- Overlaps in epidemiologic and clinical aspects of shared risk factors for AD and cardiovascular diseases
- The impact of vascular burden of AD not only a risk factor but also a postdiagnostic cognitive decline factor
- The underlying mechanisms between vascular risk factors and brain pathology in AD need to be further investigated
Thank you for your attention!!