Gothenburg MCI study report – now and in the future

9th Panhellenic Conference on Alzheimer’s disease,
Thessaloniki, 14 May 2015

Anders Wallin
Gothenburg
Sweden
anders.wallin@neuro.gu.se
Memory clinic in Moelndal
Clinical setting.
How our research at the memory clinic is organized

- Patient care
- Investigator driven clinical research
- Sponsored trials
Predecessors of Gothenburg MCI study

- Prospective dementia study (1987-1991)
- Revised prospective dementia study (1991-1997)

Gothenburg MCI study started 2000 (Dec 1999) and is ongoing
Primary aims of the Gothenburg MCI study

Investigate Alzheimer’s disease, subcortical vascular disease and their combinations among patients seeking help for cognitive complaints at a memory clinic

(1) The distributions of the diseases

(2) The characteristics of the diseases
Secondary aims of the Gothenburg MCI study

(1) Identify factors and patterns that predict development of dementia among patients with subjective or mild cognitive impairment in a memory clinic population

(2) Characterize the course of the disease(s)

(3) Develop low tech cognitive assessment methods
Design

• Inclusion/exclusion criteria
• Diagnostics
• Independent methods
  – Psychometrics
  – Neurochemistry
  – Neuroimaging/Physiological methods
  – Blood chemistry
  – Genetics
• Repeated measurements
Diagnostics

• Assessment of acquired cognitive impairment
  Global Deterioration Scale 2-4
  • STEP
  • I-Flex
  • MMSE
  • CDR

• Diagnostics of phenotypically specific dementia diseases
  AD/Mixed type dementia/Subcortical vascular disease
  • Brain regional syndrome (frontosubcortical, parietal)
  • White matter changes (mild, moderate, severe)

• Vascular burden
  Yes/No
  • Vascular risk factors and diseases
  • Brain imaging changes
## Similar clinical studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gothenburg MCI study</td>
<td>Monocenter explorative clinical-pathophysiological study dealing with early and manifest phases of the AD – subcortical vascular disease spectrum in a memory clinic setting</td>
</tr>
<tr>
<td>Alzheimer’s Disease Neuroimaging Initiative (ADNI) study</td>
<td>No explicit focus on the subcortical vascular part; search for biomarker cut-offs for trials; multicenter study</td>
</tr>
<tr>
<td>Australian Imaging Biomarkers Lifestyle (AIBL) study</td>
<td>No explicit focus on the subcortical vascular part; lifestyle issues; multicenter study</td>
</tr>
</tbody>
</table>
Results
Characterization of participants of the Gothenburg MCI study springtime 2014

<table>
<thead>
<tr>
<th>Baseline</th>
<th>All patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>664</td>
<td>115</td>
</tr>
<tr>
<td>Male/female</td>
<td>275/389</td>
<td>44/71</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>64.8 (7.9)</td>
<td>64.4 (6.4)</td>
</tr>
<tr>
<td>Mean years of education (SD)</td>
<td>12.1 (3.7)</td>
<td>11.9 (3.0)</td>
</tr>
<tr>
<td>Mean MMSE (SD)</td>
<td>27.4 (2.5)</td>
<td>29.3 (0.9)</td>
</tr>
</tbody>
</table>
Table 3. Baseline syndromal and etiological diagnoses of the Gothenburg MCI study

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Healthy</th>
<th>SCI</th>
<th>MCI</th>
<th>Dementia</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>-</td>
<td>195</td>
<td>274</td>
<td>195</td>
<td>664</td>
</tr>
<tr>
<td>Male/female</td>
<td>-</td>
<td>82/113</td>
<td>110/164</td>
<td>83/112</td>
<td>275/389</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>-</td>
<td>61.8 (7.6)</td>
<td>65.2 (7.7)</td>
<td>67.3 (7.4)</td>
<td>64.8 (7.9)</td>
</tr>
<tr>
<td>Mean years of education (SD)</td>
<td>-</td>
<td>13.6 (3.6)</td>
<td>11.8 (3.5)</td>
<td>11.0 (3.5)</td>
<td>12.1 (3.7)</td>
</tr>
<tr>
<td>Mean MMSE (SD)</td>
<td>-</td>
<td>29.1 (0.9)</td>
<td>28.0 (1.5)</td>
<td>24.8 (2.7)</td>
<td>27.4 (2.5)</td>
</tr>
<tr>
<td>AD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>81</td>
<td>-</td>
</tr>
<tr>
<td>SVD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>27</td>
<td>-</td>
</tr>
<tr>
<td>Mix</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>41</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>46</td>
<td>-</td>
</tr>
</tbody>
</table>
Characterization of early and late cohorts of the Gothenburg MCI study

<table>
<thead>
<tr>
<th>Cohorts:</th>
<th>2000-2006</th>
<th>2007-2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>401</td>
<td>263</td>
</tr>
<tr>
<td>Male/female</td>
<td>171/230</td>
<td>104/159</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>64.2 (7.7)</td>
<td>65.7 (8.0)</td>
</tr>
<tr>
<td>Mean years of education (SD)</td>
<td>11.6 (3.7)</td>
<td>12.8 (3.5)</td>
</tr>
<tr>
<td>Mean MMSE (SD)</td>
<td>27.5 (2.5)</td>
<td>27.2 (2.4)</td>
</tr>
</tbody>
</table>
# Inclusion percentage and characterization of not included patients at the memory clinic 2010-2012

<table>
<thead>
<tr>
<th>Reason</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included</td>
<td>99</td>
<td>10%</td>
</tr>
<tr>
<td>Patient declines</td>
<td>73</td>
<td>7%</td>
</tr>
<tr>
<td>Age</td>
<td>178</td>
<td>17%</td>
</tr>
<tr>
<td>Healthy</td>
<td>68</td>
<td>7%</td>
</tr>
<tr>
<td>Dementia</td>
<td>62</td>
<td>11%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>118</td>
<td>11%</td>
</tr>
<tr>
<td>Neurologic disorders</td>
<td>20</td>
<td>2%</td>
</tr>
<tr>
<td>Systemic disorders</td>
<td>30</td>
<td>3%</td>
</tr>
<tr>
<td>Vascular/met disorders</td>
<td>56</td>
<td>7%</td>
</tr>
<tr>
<td>Foreign language.</td>
<td>19</td>
<td>2%</td>
</tr>
<tr>
<td>Referral to other clinics</td>
<td>4</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td>“Unclear”</td>
<td>81</td>
<td>8%</td>
</tr>
<tr>
<td>No information</td>
<td>205</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1030</strong></td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Conversion after 6 years for patients with SCI or MCI at baseline

<table>
<thead>
<tr>
<th>Year 6</th>
<th>N</th>
<th>%</th>
<th>SCI at baseline N 195</th>
<th>%</th>
<th>MCI at baseline N 274</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total conversion n (%)</td>
<td>69</td>
<td>23.6%</td>
<td>6</td>
<td>5.3%</td>
<td>63</td>
<td>35.2%</td>
</tr>
<tr>
<td>To AD N (%)</td>
<td>29</td>
<td>9.9%</td>
<td>2</td>
<td>1.8%</td>
<td>27</td>
<td>15.1%</td>
</tr>
<tr>
<td>To SVD N (%)</td>
<td>16</td>
<td>5.5%</td>
<td>4</td>
<td>3.5%</td>
<td>12</td>
<td>6.7%</td>
</tr>
<tr>
<td>To Mix N (%)</td>
<td>15</td>
<td>5.1%</td>
<td>0</td>
<td>0.0%</td>
<td>15</td>
<td>8.4%</td>
</tr>
<tr>
<td>To other N (%)</td>
<td>8</td>
<td>2.7%</td>
<td>0</td>
<td>0.0%</td>
<td>8</td>
<td>4.5%</td>
</tr>
</tbody>
</table>
Neuropathological assessment in subjects with dementia

<table>
<thead>
<tr>
<th>Study</th>
<th>Vascular lesions</th>
<th>Mixed pathology</th>
<th>Alzheimer’s pathology</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honolulu-Asia Aging study</td>
<td>24%</td>
<td>45%</td>
<td>20%</td>
<td>Petrovitch et al., 2005</td>
</tr>
<tr>
<td>Vienna</td>
<td>8%</td>
<td>24%</td>
<td>46%</td>
<td>Jellinger &amp; Neumayer, 1964</td>
</tr>
<tr>
<td>Hisayama study</td>
<td>29.5%</td>
<td>4.7%</td>
<td>45.1%</td>
<td>Matsui et al., 2009</td>
</tr>
</tbody>
</table>

From H. Tomimoto / Neuroscience Research 71 (2011) 193–199
Further examination declined after 6 years for patients with SCI or MCI at baseline

<table>
<thead>
<tr>
<th>Year 6</th>
<th>N 469</th>
<th>%</th>
<th>SCI at baseline N 195</th>
<th>%</th>
<th>MCI at baseline N 274</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further examination declined N (%)</td>
<td>75</td>
<td>25.7%</td>
<td>32</td>
<td>28.3%</td>
<td>43</td>
<td>24.0%</td>
</tr>
<tr>
<td>No information N (%)</td>
<td>42</td>
<td>14.4%</td>
<td>19</td>
<td>16.8%</td>
<td>23</td>
<td>12.8%</td>
</tr>
</tbody>
</table>
Neuropsychology
Different cognitive profiles between AD and subcortical vascular disease also in early phases
Neuroimaging
Apathy is a prominent neuropsychiatric feature of radiological white-matter changes in patients with dementia.

Jonsson M, Edman A, Lind K, Rolstad S, Sjögren M, Wallin A

Neuroimaging

*Take home message*
Reduced hippocampal size is not necessarily a sign of Alzheimer’s disease

High white matter lesion load is associated with hippocampal atrophy in mild cognitive impairment.
Neurochemistry
Alzheimer subcortical vascular dementia spectrum – possible pathogenetic pathways

Alzheimer’s disease

Ischemia/Hypoxia
Damage to neurovascular unit

Reactive gliosis

↑Proinflammatory cytokines
↑Matrix metalloproteinases

Neuronal and oligodendroglial/axonal damage

Aβ dysmetabolism
Impaired clearance

CAA

BBB

Subcortical vascular dementia
A characteristic neurochemical CSF pattern in patients with subcortical vascular disease

Bjerke, Wallin et al, 2011
A characteristic neurochemical CSF pattern in patients with subcortical vascular disease

- Alzheimer
- Mixed dementia
- Subcortical vascular disease/dementia

Abeta1-42 and amyloid-related markers

- t-tau
- p-tau

Vascular changes

- nfl, mbp, timp-1, mmp-9

Alzheimer changes

Bjerke, Wallin et al, 2011
Prediction
Proportion non demented

Time in months

T-tau/Aβ42 & HCV & TMT B -
T-tau/Aβ42 & HCV & TMT B +

Eckerström et al 2014
Cognitive reserve and course of the disease
Biomarkers in Relation to Cognitive Reserve in Patients with Mild Cognitive Impairment – Proof of Concept

S. Rolstad  A. Nordlund  C. Eckerström  M.H. Gustavsson  H. Zetterberg  A. Wallin

Institute of Neuroscience and Physiology, Sahlgrenska Academy at Göteborg University, Mölndal, Sweden
Table 4. Baseline data for MCI patients converting to dementia at the subsequent 2-year follow-up grouped with 15 years as cut-off for higher educational attainment

<table>
<thead>
<tr>
<th></th>
<th>MCI-con</th>
<th>Adjusted p</th>
<th>Partial η²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥15 years (n = 9)</td>
<td>&lt;15 years (n = 48)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>68.4 ± 6.9</td>
<td>66.4 ± 7.2</td>
<td>NS (unadj.)</td>
</tr>
<tr>
<td>Education, years</td>
<td>16.4 ± 2.1</td>
<td>9.5 ± 2.3</td>
<td>0.0005</td>
</tr>
<tr>
<td>MMSE score</td>
<td>27.6 ± 1.9</td>
<td>27.5 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>t-tau, ng/l</td>
<td>796.7 ± 450.6</td>
<td>613.7 ± 469.6</td>
<td>NS</td>
</tr>
<tr>
<td>Aβ42, ng/l</td>
<td>372.8 ± 113.5</td>
<td>510.0 ± 153.9</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Values are means ± standard deviations. Significance levels (p) are adjusted for age; NS = not significant. Partial η² = Effect size; t-tau = CSF total tau; Aβ42 = CSF Aβ42.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Dependent variable</th>
<th>Predictor</th>
<th>Beta</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDS 2</td>
<td>Visuospatial</td>
<td>NF-L</td>
<td>-.54</td>
<td>-3.55</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Attention/speed</td>
<td>NF-L</td>
<td>-.58</td>
<td>-4.46</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td></td>
<td>Executive functions</td>
<td>NF-L</td>
<td>-.46</td>
<td>-3.10</td>
<td>.004</td>
</tr>
<tr>
<td>GDS 3</td>
<td>Attention/speed</td>
<td>NF-L</td>
<td>-.38</td>
<td>-3.25</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>Executive decline</td>
<td>NF-L</td>
<td>-.44</td>
<td>-3.04</td>
<td>.004</td>
</tr>
<tr>
<td>GDS 4</td>
<td>Memory</td>
<td>Aβ1-42</td>
<td>-.46</td>
<td>3.69</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Memory decline</td>
<td>Aβ1-42</td>
<td>.50</td>
<td>2.95</td>
<td>.007</td>
</tr>
<tr>
<td></td>
<td>Executive decline</td>
<td>Aβ1-42</td>
<td>.51</td>
<td>3.17</td>
<td>.005</td>
</tr>
</tbody>
</table>

NF-L = neurofilament light subunit, Aβ1-42 = amyloid beta 1-42, GDS = Global Deterioration scale

Rolstad et al, 2015
Low tech cognitive assessment
Cognitive Assessment Battery, CAB

Patientdata

Name: .................................................................
Veren:.................................................................
Amdal: .................................................................

Testerna analyserades av: ...........................................

Nordlund, Wallin et al., 2011
SASCI-Q – measurement of subjective cognitive impairment

Sahlgrenska Academy Self-reported Cognitive Impairment Questionnaire (SASCI-Q) – a research tool discriminating between subjectively cognitively impaired patients and healthy controls

Marie Eckerström,¹ Johanna Skoogh,² Sindre Rolstad,¹ Mattias Göthlin,¹ Gunnar Steineck,² Boo Johansson³ and Anders Wallin¹

¹Institute of Neuroscience and Physiology, the Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
²Department of Oncology, Division of Clinical Cancer Epidemiology, Institute of Clinical Sciences, the Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
³Department of Psychology, University of Gothenburg, Gothenburg, Sweden
SASCI-Q

• SASCI-Q – specially developed to measure subjective cognitive impairment
• Satisfying psychometric properties
• Discriminates between healthy controls and patients with SCI
• A valid tool for future longitudinal examinations of the SCI group
Cognitive Impairment Questionnaire (CIMP-QUEST)

Alzheimer and Subcortical Vascular Disease in a Hospital-Based Setting: Review of Results from the Gothenburg MCI Study

Anders Wallin¹, Arto Nordlund¹, Michael Jonsson¹, Kaj Blennow¹, Henrik Zetterberg¹,², Annika Öhrfelt¹, Jacob Stålhammar¹, Marie Eckerström¹, Märten Carlsson¹, Erik Olsson¹, Mattias Göthlin¹, Johan Svensson⁴, Sindre Rolstad¹, Carl Eckerström¹

¹ Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden
² The Torsten Söderberg Professorship at the Royal Swedish Academy of Sciences
³ UCL Institute of Neurology, Queen Square, London, UK
⁴ Institute of Medicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
Gothenburg MCI study: Conclusion and Impact

• It is possible to identify Alzheimer’s disease and subcortical vascular disease in a memory clinic setting
• The number of patients with subcortical vascular disease is not insignificant
• Neuropsychological, neurochemical and course profile differences have been found between Alzheimer’s disease and subcortical vascular disease
• Although the results need to be replicated they should already now be taken into account in the design of clinical trials and clinical practice
• Our results demonstrate that Gothenburg MCI study is a valuable link between preclinical and epidemiological research
Gothenburg MCI study: Next STEP

- Inclusion and follow-up strategies
- New studies
  - Neurochemistry
  - SPECT
  - Metabolic
  - Rheological
  - Endocrine
- MR/PET
- Big data analyses
- Multicenter studies on subcortical vascular disease; SCI
- Modern medicine
- Center of Cognitive Medicine
How clinical research may be accomplished – experiences from research at the memory clinic

Centre for cognitive medicine

By a common network the research forms a bridge and fertilizes/is fertilized by other clinical and other fields

- Dementia research
- Special knowledge in cognition
- Knowledge/experiences from other clinical and other fields
- Centre for cognitive medicine
  - Stroke
  - Stress
  - Heart-vessel
  - Infection
  - Psychiatry
  - etc.
Cognitive medicine – definition

A field that deals with

- Identification of cognitive impairment
- Linking cognitive impairment to the whole range of medical conditions
- Intervention
The Center of Cognitive Medicine Initiative: Sustaining cognition in a changing society

Wallin et al, 2014
www.kognitivmedicin.se
Thanks for your collaboration and attention!
Our clinical and other studies/projects

- Centre of Cognitive Medicine Initiative; Gothenburg MCI study: Early diagnosis and treatment options in AD and subcortical vascular disease
- Swedish Brain Power (SBP): Early diagnosis and treatment options in neurodegenerative disorders
- SCAPIS (Swedish CardioPulmonary bioImage Study). Vascular risk factors and vessel wall imaging of the cardiovascular system in healthy people between 50 and 65 years of age
- MedCoast GO-MCI (Göteborg-Oslo MCI study): Early diagnosis and treatment options in patients with vascular cognitive disorders
- LeukoAraisois and DISability in the elderly, LADIS: The effect of white matter changes on disability
- NILVAD. European multicenter double-blind controlled phase 3 study with the calcium blocker nilvadipine
- EMIF (European Medical Information Framework). Data mining project to clarify characteristics of early phases of AD and metabolic diseases
Acknowledgement

Clinical research group

Researchers
Anne I Berg
Maria Bjerke
Carl Eckerström
Michael Jonsson
Arto Nordlund
Erik Olsson
Helge Malmgren
Sindre Rolstad
Johan Svensson
Annika Öhrfelt
Anders Wallin

Research students
Marie Eckerström
Mattias Göthlin
Mårten Karlsson
Niklas Klasson
Sara Remdahl
Jacob Stålhammar

Research Staff
Carina Andersen
Eva Bringman
Ing-Marie Isgaard
Marie Johansson

Neurochemistry
Kaj Blennow
Henrik Zetterberg
and others

Neuropsychology
Boo Johansson
and others

Swedish Brain Power
Bengt Winblad
and others

MedCoast
Tormod Fladby
Erik Hessen
and others

LADIS
Domenico Inzitari
Leonardo Pantoni
and others

NILVAD
Brain Lawlor
and others

EMIF
Pieter J Visser
and others

Research group on cognitive disorders
Sahlgrenska University Hospital,
Gothenburg, Sweden