Down Alzheimer Barcelona Neurimaging Initiative (DABNI):
A Trial Ready Cohort to Study Alzheimer Biomarkers in Down Syndrome

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Hospital of Sant Pau and Fundació Catalana Síndrome de Down
AD is the main medical problem in adults with DS (and cause of death)

Life expectancy (Australia)

AD prevalence (New York)

3 copies of the APP gene are enough to cause presenile AD dementia


Bittles, Glasson et al. 2004

DABNI: A research project based on a Health Plan

First Population based AD screening program in DS

ANNUAL MEDICAL ASSESSMENT
Neurology/ Neuropsychology
Blood test/ EEG

From 2014

CSF study
Structural, functional MRI
FDG-PET Florbetapir-PET Tau-PET
Polysomnography

DABNI
Clinical Results
Cross sectional data

From May 2014 to April 2017

N=434

- Without cognitive impairment
- Questionable dementia
- Alzheimer type dementia
- Psychiatric etiology

[Bar chart showing age distribution and categories of cognitive impairment]
Longitudinal one year data (N=235)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline n=235</th>
<th>Baseline %</th>
<th>Follow-up n=235</th>
<th>Follow-up %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>170</td>
<td>72,3%</td>
<td>159</td>
<td>67,7%</td>
</tr>
<tr>
<td>Prodromal AD</td>
<td>26</td>
<td>11,1%</td>
<td>20</td>
<td>8,5%</td>
</tr>
<tr>
<td>Established AD</td>
<td>27</td>
<td>11,5%</td>
<td>44</td>
<td>18,7%</td>
</tr>
<tr>
<td>TNC</td>
<td>12</td>
<td>5,1%</td>
<td>12</td>
<td>5,1%</td>
</tr>
</tbody>
</table>
CSF biomarker Results
Feasibility of Lumbar Puncture in the Study of Cerebrospinal Fluid Biomarkers for Alzheimer’s Disease in Subjects with Down Syndrome

Maria Carmona-Iragui\textsuperscript{a,b,c}, Telma Santos\textsuperscript{d}, Sebastian Videla\textsuperscript{b,e}, Susana Fernandez\textsuperscript{2}, Bessy Benejam\textsuperscript{b}, Laura Videla\textsuperscript{b}, Daniel Alcolea\textsuperscript{b,c}, Kaj Blennow\textsuperscript{f}, Rafael Blesa\textsuperscript{b,c}, Alberto Lleo\textsuperscript{b,c} and Juan Fortea\textsuperscript{a,b,c,e}

Results: There were no adverse events in 90% of our participants. The most frequent complication was headache (6.25%); only one subject reported a typical post-lumbar puncture headache with moderate severity that required analgesic treatment. Dizziness (3.75%) and back pain (1.25%) were also reported. All the participants that reported complications belonged to the active group.
Core AD CSF biomarkers: Congruent with a “Genetically determined AD”

<table>
<thead>
<tr>
<th>N=86</th>
<th>Without cognitive impairment</th>
<th>pAD or AD dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td>Age, mean (sd)</td>
<td>36.8 (9.2)</td>
<td>52.3 (6)</td>
</tr>
<tr>
<td>Gender (%male)</td>
<td>58%</td>
<td>55.6%</td>
</tr>
</tbody>
</table>

CSF-Aβ42 (pg/mL)  
$r=-0.666$  
$p<0.001$

CSF-Tau (pg/mL)  
$r=0.579$  
$p<0.001$

CSF-pTau (pg/mL)  
$r=0.567$  
$p<0.001$
Core AD CSF biomarkers: Useful in diagnosis

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF-Aβ42</td>
<td>0.911</td>
</tr>
<tr>
<td>CSF-Tau</td>
<td>0.863</td>
</tr>
<tr>
<td>CSF-pTau</td>
<td>0.819</td>
</tr>
<tr>
<td>Ratio Tau/Aβ42</td>
<td>0.932</td>
</tr>
</tbody>
</table>
Core AD and other CSF biomarkers

- **Asymptomatic subjects**
  - CSF-Aβ42 (pg/mL)
  - CSF-Aβ40 (pg/mL)
  - CSF-Tau (pg/mL)
  - CSF-pTau (pg/mL)
  - CSF-BACEact (ΔUF/min)
  - CSF-sAPPβ (ng/mL)
  - CSF-YKL40 (ng/mL)
  - CSF-NFL (pg/mL)

- **AD Symptomatic subjects**
  - CSF-Aβ42 (pg/mL)
  - CSF-Aβ40 (pg/mL)
  - CSF-Tau (pg/mL)
  - CSF-pTau (pg/mL)
  - CSF-BACEact (ΔUF/min)
  - CSF-sAPPβ (ng/mL)
  - CSF-YKL40 (ng/mL)
  - CSF-NFL (pg/mL)

*p* < 0.05
Neuroimaging Results
MRI: Same AD vulnerable areas

<table>
<thead>
<tr>
<th>N=68</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>41.4 (11.1)</td>
</tr>
<tr>
<td>Sex (F,%)</td>
<td>32.3%</td>
</tr>
<tr>
<td>Non-cognitive impairment/ Prodromal AD/ AD Dementia (%)</td>
<td>76.5/ 14.7/ 8.8</td>
</tr>
</tbody>
</table>

Unpublished data. Manuscript in preparation
FDG-PET: “AD hypometabolism”

<table>
<thead>
<tr>
<th></th>
<th>N=50</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>41.6 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Sex (F,%)</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Non-cognitive impairment/ AD group (%)</td>
<td>60/40</td>
<td></td>
</tr>
</tbody>
</table>

*Unpublished data. Manuscript in preparation*
Florbetapir PET

- 100% AD dementia and prodromal AD
- 29.4% in those without CI

40 yo man
No cognitive impairment

45 yo man
Prodromal AD

53 yo man
AD dementia
Collaborations and Current Projects
Projects on modifiable risk factors to reduce the impact of dementia:

Sleep study: To assess the impact of sleep problems on the onset of dementia. Sandra Giménez and Anne-Sophie Rebillat

Horizon 21 Genetics Consortium
Funded by J-L Institute
PI: Drs. Duijn and Coppus

AD Biological correlates in DS
Funded by NIH
PI: Dr. Granholm (U. of Denver)

DS1000: A European Trial Ready Cohort
Funded by Welcome Trust
PI: Dr. A Strydom (UCL, UK)

Inflammation and NGF Dysfunction in the Evolution of AD Pathology in DS
Drs. Cuello, Busciglio, Wisniewski, Iulita (multicenter)

Improving AD care in adults with Down syndrome
Submitted to GBHI & Alzheimer’s Association Pilot Award

Papers with International Collaborations

Alzheimers Dement. 2016;2:49-57


Cortex. 2015;73:36-61
Cerebral amyloid angiopathy

Carmona-Iragui M*, Balasa M*, et al.
In press in Alzheimer & Dementia

Conclusions of the work:

CAA is more frequent in ADAD and DS than in SAD
APOE-ε4 genotype is associated with AD and CAA in SAD, but not in ADAD or DS
CSF-Aβ40 do not differ between subjects with and without CAA
Research in Down syndrome

“Virtous Cicle”
Bidirectional flux of information

Sporadic AD ↔ AD in DS

NIH has recently invested 37 million dollars
TAKE HOME MESSAGES

1. Alzheimer’s Disease in the main medical problem and cause of death in adults with Down Syndrome

2. Research in Down Syndrome is essential to enhance their quality of life and it is a unique research opportunity: HELP THEM HELP US!

3. Europe is in a very good position to lead the research in this area:
   1. Because we have the foundations and much larger numbers
   2. Because of our health system
   3. Because we have the scientists and the will to do it

Not to perform research in people with Down Syndrome is a new form of discrimination

Down Alzheimer Barcelona Neuroimaging Initiative:
A Research Effort against AD in DS
Thank you

Participants and their families

Memory Unit - Alzheimer Laboratory
Hospital de Sant Pau

Juan Fortea Sebastiá Videla Bessy Benejam Susana Fernández Laura Videla María Carmona Iragui Daniel Alcolea Roser Ribosa Federic Sampedro Olivia Belbin Eduard Vilaplana Oriol Dols Jordi Pegueroles Martí Colom Raúl Núñez Laia Muñoz Jordi Clarimon Marta Querol Laura Cervera Estrella Morenas Isabel Sala Belén Sánchez Andrea Subirana Paula González Rafael Blesa Alberto Lleó

Gracias

Alzheimer and Down Unit
FCSD

Down Alzheimer Barcelona Neuroimaging Initiative
Plan de salud para personas con SD

Medicina terciaria

Centro médico Down

Medicina primaria

Atención terciaria

PRRECLINICAL AD

PRODROMAL AD

LOMEDS

Otros especialistas

Médico referencia: MI

Médico referencia: Neurólogo

Enfermedades comunes, vacunas...