Research Update

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Update on Alzheimer Research: Are we closer to the Holy Grail?

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Holy Grail Legend
• A cup or dish or bowl that drinking or eating from it would provide eternal youth, health, and happiness.

From http://www.bl.uk/onlinegallery/features/mythical/graalge.html

Auguste D: The First Clinical and Pathological Description of Alzheimer’s Disease (1906)

- Memory:
  • Forgetful
  • Cannot navigate around her house
- Language:
  • Paraphasic errors
  • Comprehension problems
- Orientation
  • Perplexed in the hospital
  • Disoriented to time/place
- Behaviour
  • Yelling loudly that she was about to be murdered
  • Other neurological features
  • Normal gait and strength
- Auguste D died 4.5 years later (1906)
Amyloid Plaques & Neurofibrillary Tangles

Current Diagnosis of Alzheimer (McKhann 2011)

• Symptoms of:
  • Cognitive decline: Memory, Language, Decision Making, Visuospatial, Motor planning skills, behavioural change
  • Progressive decline from previous level
  • Severe enough to affect daily function
  • No evidence of other medical, psychiatric, or neurological conditions
• Evidence of biomarkers for
  • Amyloid pathology
  • Neurodegeneration

Clinical Utilities of Biomarkers

1. Confirm the presence of a pathology
2. Differentiate between different types of dementia
3. Help to identify cases in the earliest stage (for earlier treatment and planning)
4. Follow treatment progress: cognitive assessment is quite variable in the short term and for single episode

Biomarkers are needed to improve diagnostic accuracy of patients with dementia

• Patient’s diagnosed by clinical criteria alone may not have Alzheimer Pathology

In the subgroup with PIB-PET scan available, 6.5% of APOE e4 carriers and 36.1% of non-APOE e4 carriers were “negative” on the PIB-PET scan, suggesting that they do not have amyloid pathology in the brain.

From: Salloway et al, NEJM 2014

Dementia from Different Pathologies have similar presentations

Dementia from the same pathology have variable clinical presentations
Biomarkers for Early Diagnosis: Data from the DIAN study

Current Biomarkers in AD
- Cerebral Spinal Fluid tests
  - Aβ, total tau, P181-tau, P231-tau, or combo
- Blood tests
  - (still in research?)
- Neuroimaging
  - MRI – structural / functional
  - SPECT
  - PET – FDG, PIB, AV45 & other amyloid ligands, AV1451 & tau ligands
- Genetics: mutations vs. risk factors
- Specific memory tests (& Neuropsychological tests)

CSF Biomarkers in AD
- CSF amyloid, marker of amyloidosis, drops in the early phase of AD – due to precipitation in neuritic plaques
- CSF total tau, marker of neuronal degeneration, increases throughout disease course – higher level correlates with faster cognitive decline
- CSF phosphorylated tau, is specific for AD

Other Fluid Biomarkers in dementia research
1. Markers of Amyloidosis: Aβ42, Aβ40
2. Markers of Neuronal Injury: Total tau, Phosphorylated tau, Neurofilament (NFL)
3. Marker of Synucleinopathy: α-synuclein
5. Markers of Inflammation: Monocyte chemoattractant protein 1 (MCP-1), chitinase-3-like protein (YKL-40), Visinin-like protein 1 (VLP-1)
6. Marker of synaptic degeneration: Neurogranin
7. Mass Spectroscopy instead of immunometric based measures
8. Exosomal fractions measurements

MRI brain scan as a Biomarker
- R/O stroke, tumour, bleed, white matter disease…
- Atrophy = neurodegeneration
- Structural:
  - T1, DTI, PD, GRE T2*, SWI
- Functional:
  - MR-SPECT, BOLD rs fMRI, ASL
**PET imaging in Dementia**

- FDG-PET
- Amyloid Ligands
  - $^{11}$C-PiB (Pittsburgh compound B)
  - $^{11}$C-NAV4694
  - $^{18}$F-Florbetapir (AV-45)
  - $^{18}$F-Flutemetamol
  - $^{11}$C-Florbetaben
- Tau Ligands
  - $^{18}$F-T807, AV-1451
  - $^{18}$F-THK5117
  - $^{11}$C-PBB3

**Current amyloid PET biomarkers for AD**

FDA approved (but not covered by Medicare or most insurance)

**PBB3 Tau PET correlate better than Amyloid PET with cognitive decline**

- Follows the pattern of spreading pathology of tau in AD (Braak staging)
- Appears to show tau deposits in CBD as well

From Maruyama et al, Neuron 2013
### AV1451 Tau PET in aging and early Alzheimer disease

**Pros and Cons of PET scans vs. MRI vs. CSF**

<table>
<thead>
<tr>
<th>Pros</th>
<th>PET</th>
<th>MRI</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Expensive</td>
<td>Very Limited availability (both tracer production and scanner)</td>
<td>Somewhat limited availability</td>
<td>Relatively cheap</td>
</tr>
<tr>
<td>Somewhat costly</td>
<td>May be quantitative</td>
<td>Somewhat limited availability</td>
<td>Can measure multiple pathologies at once</td>
</tr>
<tr>
<td>Relatively cheap</td>
<td>Provide detailed anatomical information</td>
<td>May be quantitative</td>
<td></td>
</tr>
<tr>
<td><strong>Cons</strong></td>
<td>Radioactive</td>
<td>No metal in body (excludes pacemakers)</td>
<td>Needle</td>
</tr>
<tr>
<td>Radioactive</td>
<td>1 tracer at a time</td>
<td>Non-specific to pathology</td>
<td>Skills of clinician</td>
</tr>
<tr>
<td>Needle</td>
<td>Long (up to 2 hrs per scan)</td>
<td>Claustrophobic</td>
<td>Difficult with back problems</td>
</tr>
</tbody>
</table>

### Clinical Trials and Use of Biomarkers

- Most newer clinical trials on Alzheimer since 2012 requires the use of Biomarkers as inclusion criteria
- A4 - Anti-Amyloid treatment in Asymptomatic Alzheimer Disease
- DIAN - Dominantly Inherited Alzheimer Network
- AMARANTH, CREAD, ENGAGE

### Some results from recent AD trials

- TauRx LMTM
- Solanezumab monoclonal antibody against Abeta
- Aducanumab monoclonal antibody against Abeta
Data presented at the CTAD meeting 2016

Solanezumab: monoclonal antibody against Abeta (Eli Lilly)
No statistically significant separation between solanezumab and placebo on the ADAS-Cog14. There was a trend of the treatment group experiencing 11% less cognitive decline than did the placebo group, but not significant (P = 0.095).

Secondary outcome: MMSE showed a 13% slowing of decline compared to placebo (P = 0.014), and a 5% difference in the Clinical Dementia Rating scale-sum of boxes test (P = 0.004).

Safety: 17% of treatment group reported an adverse event, vs. 19% of placebo patients. There were 9 deaths in the solanezumab arm and 16 in the placebo arm.

(Current debate: dose problem, target problem, timing problem?)

Aducanumab Study (Biogen)
Sevigny Nature 2016

Some current Clinical Trials at UBCH CARD
1. A4: for subjects over age 65, cognitively normal, but screened positive by Amyloid PET
2. Biogen aducanumab: for biomarker positive MCI or mild AD
3. Roche crenezumab: for biomarker positive MCI or mild AD
4. AMARANTH BACE1 inhibitor: for MCI or mild AD (MMSE 21-28) who are PET or CSF positive for amyloid
5. A MINT: study effect of fatty acid (i.e. coconut oil) in mild to moderate AD
6. DIAN-TU: for subjects at-risk for carrying a gene for Early-Onset Alzheimer (active, a third arm to be added)
7. Upcoming prevention study based on APOE, treatment based on tau monoclonal antibody

Other non-drug approaches (better for prevention than treatment)
1. Exercise: aerobic (e.g. walk, swim) and resistance (e.g. weights)
2. Cognitive stimulation (don’t just sit and watch TV: read, socialize, play games, music – sing and dance)
3. Diet (Mediterranean: less fat and red meat, more fish, nuts, and fruits and vegetables)
4. Most recent study suggests even moderate alcohol consumption is bad for brain.

1. Preserve general health (less other medical problems and medications, less complications)

FINGER study: Ngandu Lancet 2015 vs. MAPT study: Andrieu Lancet Neuro 2017

Developments in non-AD dementias
1. Frontotemporal Dementia:
   - New gene identified for FTD
   - New targets for progranulin and TDP-43
2. Synucleinopathy (Parkinson and Lewy Body): strongly associated with sleep abnormalities
3. Most strokes are preventable (control blood pressure, blood sugar, cholesterol, heart disease)

The Conundrums of Biomarkers and Treatment of AD
• Full validation of the dementia biomarkers require autopsy studies
• Definition of "asymptomatic" Alzheimer Disease
• Revealing results to patients / subjects: lessons from predictive genetic testing
• Successful treatment requires highly accurate biomarkers
• Does not rule out "mixed pathology", unless biomarkers for every other pathologies are also available
Summary

• Have we found the Holy Grail to preserve mental function? Getting quite close with predicting outcome, but not so close with treatment ...

• Paradigm shift - from diagnosis based on symptoms to predicting outcome based on biomarkers

• Pros - easier to prevent than to treat
• Cons - the prediction must be correct, and the preventive treatment must be safe

• More studies are needed to fully understand how to properly use these biomarkers

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Many others……

Support from the Ralph Fisher & Alzheimer Society of BC Professorship in Alzheimer’s Research

Alzheimer Society of B.C.
Programs and Services

Alzheimer Resource Centres
for information, education, support and referrals.

First Link® Dementia Helpline
1-800-936-6033 (Lower Mainland)
604-681-8651 (Lower Mainland)

Minds in Motion®
Weekly exercise and social program for people with early symptoms of dementia and a care partner.

Support groups
• For people with early symptoms
• For care partners

Education
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• Shaping the Journey: living with dementia®
• Family Caregiver Series
• Transition to Residential Care
• Dementia Dialogues
• Tele-workshops

Information bulletins
• First Link® Bulletin
• Connections
• Insight for people with dementia

Website
www.alzheimerbc.org

Provincial Office (to order handouts/bulletins)
1-800-667-3742 or
604-681-6530

Website
www.alzheimerbc.org

First Link® Dementia Helpline
1-800-936-6033 or
604-681-8651

Newsletters

Connections
A quarterly publication featuring submissions by and resources for caregivers, as well as news, updates and ways to get involved with the Society.

Insight
Educational bulletin for and by people with dementia

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Or call 604-681-6530 or 1-800-667-3742 (toll free)