Genes & Scans: the role of Biomarkers in Dementia Diagnosis

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What is a Biomarker?

- Biomarkers = a characteristic that is objectively measured and assessed as an indicator of normal biologic or pathogenic processes, or pharmacological responses to a therapeutic (US NIH, Clin Pharm Ther 2001)

- In plain English – something that can “measure” a change in a “body condition”
Common Examples of Biomarkers

Temperature

Blood pressure

Blood sugar
An Ideal Biomarker

1. Sensitive – identify all cases of the disease
2. Specific – only for the disease in question
3. Responsive – detect changes in disease or improvement with treatment
4. Accurate and precise
5. Correlate with clinical stage
6. Pathology – identify disease process
7. Safe and easy to obtain
8. Cost – as cheap as possible
Why biomarkers in Dementia?

• **Confirm** the diagnosis
• **Differentiate** between different types of dementia
• Help to identify cases in the **earliest** stage (for earlier treatment and planning)
• Follow treatment **progress**
New Diagnostic Criteria for AD

Biomarkers increases diagnostic probability of AD & MCI (prodromal AD)

1. Presence of amyloid pathology
   (PiB PET or CSF A-beta)

2. Presence of brain cells damage
   (MRI brain shrinkage, FEG-PET, or CSF tau)

McKhann 2011
Current Biomarkers

- Specific memory tests (Neuropsychology)
- Spinal Fluid tests
  - $A\beta$ and tau, or both
- Blood tests
  - (none for Alzheimer, potential for FTD)
- Neuroimaging
  - MRI
  - PET – FDG, PIB, AV45
- Genetic mutations vs. risk factors
Molecular Biomarkers in AD

• Pathology of AD involves Aβ aggregation and hyperphosphorylation of tau

• In AD, CSF Aβ42 is decreased while total and p-tau are increased, compared to controls
CSF Biomarkers in MCI

Hansson 2006
CSF Biomarkers in AD

Limitations

- Site-to-site and repeat measure variations in up to 30% (Lewczuk, Neurosci Lett 2006)
- Overlap between Normal and AD?
- Imperfect specificity
  - $\beta$ also reported to be decreased in DLB, FTD, VaD (or is it because of co-existing AD?)
  - P-tau has better specificity against FTD than other markers
Blood tests for Dementia?

- None proven for Alzheimer yet
- Serum Progranulin measurement may identify a particular type of Frontotemporal Dementia
MRI in AD

- Medial Temporal Lobe / Hippocampus atrophy

- >85% sensitivity and specificity
MRI in AD

- **Strengths**
  - Rule out other dementias (FTD, strokes, CJD, encephalitis, etc)
  - Accuracy improves when age and memory scores taken into account

- **Limitations**
  - Not sensitive in early phase
  - Variations between individuals? Standardized brain?
  - Does not correlate well with cognition
FDG-PET

- 18F-FDG PET may detect prodromal AD with accuracy of 75-84%
- Combined with impaired delayed recall scores as a clinical marker – sensitivity and specificity can be over 90%
- Limited accuracy differentiating AD vs. VaD (sensitivity 75-88%, specificity 18-53%)
PET scans in AD

- Pittsburgh Compound B (PiB) and newer ligands (AV45) may allow for visualization of amyloid deposits
- Technique is very promising, but...
- Positive in ~1/3 of normal elderly?
- Also positive in DLB & VaD? Are these mixed pathology?
- Expensive
- Limited availability
# Genetics in Dementia

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>21q21</td>
<td>APP</td>
<td>Early Onset Alzheimer</td>
</tr>
<tr>
<td>14q24.3</td>
<td>PS1</td>
<td>Early Onset Alzheimer</td>
</tr>
<tr>
<td>1q31-q42</td>
<td>PS2</td>
<td>Early Onset Alzheimer</td>
</tr>
<tr>
<td>19cen-q13.2</td>
<td>ApoE</td>
<td>Risk for Late Onset Alzheimer</td>
</tr>
<tr>
<td>11q24</td>
<td>SORL1</td>
<td>Risk for Late Onset Alzheimer</td>
</tr>
<tr>
<td>1q32</td>
<td>CR1</td>
<td>Risk for Late Onset Alzheimer</td>
</tr>
<tr>
<td>11q14</td>
<td>PICALM</td>
<td>Risk for Late Onset Alzheimer</td>
</tr>
<tr>
<td>17q21.1</td>
<td>Tau (MAPT)</td>
<td>FTDP-17</td>
</tr>
<tr>
<td>17q21.31</td>
<td>Progranulin (GRN)</td>
<td>FTLD-TDP (FTLD-U)</td>
</tr>
<tr>
<td>9p21.2</td>
<td>C9ORF72</td>
<td>FTLD-TDP &amp; ALS</td>
</tr>
<tr>
<td>9p13.3</td>
<td>VCP</td>
<td>FTD + IBM and Paget’s Disease</td>
</tr>
<tr>
<td>3p11.2</td>
<td>CHMP2B</td>
<td>FTLD-U</td>
</tr>
</tbody>
</table>

**Risk vs. mutations**
## Limitations of the Current Biomarkers

<table>
<thead>
<tr>
<th></th>
<th>Memory Tests</th>
<th>Spinal Fluid tests</th>
<th>MRI brain scan</th>
<th>PET scan</th>
<th>Genetic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simple to complex</td>
<td>Abeta, tau</td>
<td>Brain shrinkage</td>
<td>Amyloid deposits</td>
<td>Yes (only for specific types)</td>
</tr>
<tr>
<td>Sensitive</td>
<td>May be</td>
<td>Yes and No?</td>
<td>No</td>
<td>Yes (too sensitive)</td>
<td>Yes (mutation) No (risk)</td>
</tr>
<tr>
<td>Specific</td>
<td>No</td>
<td>May be? For Alzheimer</td>
<td>No</td>
<td>May be</td>
<td>Yes (mutation) No (risk)</td>
</tr>
<tr>
<td>Responsive</td>
<td>Yes</td>
<td>Probably No, but may be</td>
<td>May be</td>
<td>Probably No</td>
<td>No</td>
</tr>
<tr>
<td>Stage</td>
<td>Yes</td>
<td>No</td>
<td>Not quite</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Safe and easy</td>
<td>Yes</td>
<td>Arguably yes</td>
<td>Yes (but no metal)</td>
<td>A little radiation</td>
<td>Yes (but need psychological counseling too)</td>
</tr>
<tr>
<td>Cost</td>
<td>$0-2000</td>
<td>$100-600</td>
<td>$800-1500</td>
<td>$2500-6000</td>
<td>$500-2000</td>
</tr>
</tbody>
</table>
Where are we today?

• New criteria for Alzheimer Disease incorporated biomarkers to improve diagnostic certainty & to identify prodromal disease (Mild Cognitive Impairment)

• Up-coming Clinical Trials will likely require some, or all, of these biomarkers
Where do we go from here?

- None of the biomarkers are covered by BC Medical Services Plan (some genetic tests may get covered in the future – under negotiation)
- No single test is ideal
- Doing all the tests will be expensive
- Need more studies to learn how to best use these tests in the clinical setting
- Need even more studies to find better biomarkers
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