CSF biomarkers for dementia diagnosis

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**Biomarker: definition**

“A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention”

NIH Biomarker Definitions Working Group 1998
Biomarker: properties

Sensitive to the disease
Specific to the disease
Quantifiable
Reproducibly measured
Correlates with disease severity
Tracks response to treatment

Example: PSA – prostate cancer
Alzheimer’s disease – AT(N) definition

Aβ plaques (A)
- amyloid-PET
- low CSF Aβ$_{42}$

Fibrillar tau (T)
- tau-PET
- high CSF p-tau

Neurodegeneration (N)
- Atrophy
- FDG-PET
- CSF t-tau
Alzheimer’s disease – AT(N) definition

- **Aβ plaques (A)**
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NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease

Alzheimer’s & Dementia 14 (2018) 535-562
NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease

Text Box 2
AT(N)(C) measures have different roles for definition and staging

Definition
A: Aβ biomarkers determine whether or not an individual is in the Alzheimer’s continuum.
T: Pathologic tau biomarkers determine if someone who is in the Alzheimer’s continuum has Alzheimer’s disease.

Staging severity
(N): Neurodegenerative/neuronal injury biomarkers
(C): Cognitive symptoms

A and T indicate specific neuropathologic changes that define Alzheimer’s disease, whereas (N) and (C) are not specific to Alzheimer’s disease and are therefore placed in parentheses.
CSF biomarkers
prognostic value
60 month follow-up of MCI

### Diagnostic accuracy: Cochrane

<table>
<thead>
<tr>
<th></th>
<th>Specificity %</th>
<th>Sensitivity %</th>
</tr>
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<tbody>
<tr>
<td>t-tau</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>p-tau</td>
<td>48</td>
<td>81</td>
</tr>
<tr>
<td>p-tau/AB42 ratio</td>
<td>33-95%</td>
<td>80-96%</td>
</tr>
<tr>
<td>Amyloid-PET</td>
<td>58</td>
<td>96</td>
</tr>
<tr>
<td>MMSE &lt; 24</td>
<td>88</td>
<td>40</td>
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CSF biomarkers
utility in clinic
Diagnostic impact of CSF biomarkers for Alzheimer’s disease in a tertiary memory clinic


Alzheimer Center & Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
Department of Clinical Chemistry, Neurochemistry Laboratory and Biobank, VU University Medical Center, Amsterdam, The Netherlands
Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

N = 438, 63±8y, 39%F, MMSE 24±5
Neurologists completed questionnaires before and after CSF disclosure
Change in diagnosis, diagnostic confidence, impact on patient management
• 7% of diagnoses were changed
• Diagnostic confidence increased from 84% to 89%
Cambridge Memory Clinic audit 2017
Indication for CSF biomarkers

- Diagnosis unclear
- Diagnosis confirmation

% of patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>% of patients</th>
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<tbody>
<tr>
<td>Mood disorder</td>
<td></td>
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<tr>
<td>AD vs mood disorder</td>
<td></td>
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<tr>
<td>Other dementia</td>
<td></td>
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<tr>
<td>Complicating factors</td>
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</table>
Cambridge Memory Clinic audit 2017
Indication for CSF biomarkers

- Changed diagnosis
- Confirmed diagnosis
- Clarified diagnosis
- Diagnosis remained uncertain
- Diagnosis made on a concurrent test
- Diagnosis unchanged despite lack of support from biomarkers
Case study TS
72 years old, right handed retired physics teacher. Undergraduate degree in Physics and Chemistry then MSc in Astrophysics

March 2015: seen in general neurology clinic
   - Behavioural change
     • Irritable, short-tempered
     • More selfish
   - “poor memory”

O/E slightly unsteady walking heel-toe. Otherwise normal examination
   “extremely articulate with no detectable language dysfunction”
   above average immediate and delayed verbal recall

Diagnosis: not established
August 2015: seen in Cambridge Memory Clinic

History from patient:
Occasional “senior moment” eg entering a room and forgetting the reason for entry
Intact ability to recall details of day to day events
Less interested in hobbies eg astrophysics, optics, genealogy
No depression or anxiety, enjoys life

History from wife:
Five year history of change in personality (irritability, reduced insight, loss of empathy)
Four year history of decline in episodic memory eg for conversations, daily events
Mental inflexibility
Poor driving; difficulty keeping to motorway lanes, minor scrapes to side of car when parking
Bumps into doorways, uses finger to track lines of text when reading
TS

Normal social behaviour
Weight stable
Good general health apart from minor OA aches

No family history of AD, PD, MND, “dementia”

Non-smoker, EtOH intake low

No medication usage
On examination:
euthymic, no behavioural abnormalities
Normal speech (grammar, fluency, content)
Slight difficulty walking heel-toe
Normal eye movements, no visual disorientation
No muscle wasting/fasciculations
No extrapyramidal or cerebellar syndrome
No limb apraxia

ACE-R: 100/100
TS

Summary

72 year old man with five year history of behavioural change and subsequent impairment of episodic memory + ?mild incoordination/visuospatial problems but 100/100 on ACE-R

MRI brain normal
Neuropsychological testing

Premorbid IQ = 128
Immediate and delayed verbal memory: 75-90th %ile
Immediate and delayed nonverbal memory: 99th %ile
Graded naming test: 30/30
Category fluency: >90th %ile
Moderate impairment of executive function, eg WCST
Visual object and spatial perception: PASS
TS

CSF $\beta$-amyloid < 63 (NR 627-1372)
    Tau 386 (NR 146-395)

Diagnosis: possible prodromal Alzheimer’s disease

Follow-up:
    Progressive annual cognitive decline
    Now no longer driving
CSF biomarkers
guidelines for usage
1.2.14 Only consider further tests (recommendations 1.2.15–28) if:

- it would help to diagnose a dementia subtype and
- knowing more about the dementia subtype would change management.

**Further tests for Alzheimer's disease**

1.2.15 If the diagnosis is uncertain (see recommendation 1.2.14) and Alzheimer's disease is suspected, consider either:

- FDG-PET (fluorodeoxyglucose-positron emission tomography-CT), or perfusion SPECT (single-photon emission CT) if FDG-PET is unavailable

  or

- examining cerebrospinal fluid for:
  - either total tau or total tau and phosphorylated-tau 181 and
  - either amyloid beta 1–42 or amyloid beta 1–42 and amyloid beta 1–40.

If a diagnosis cannot be made after one of these tests, consider using the other one.
Review Article

Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer’s disease

Leslie M. Shaw\textsuperscript{a}, Jalayne Arias\textsuperscript{b}, Kaj Blennow\textsuperscript{c}, Douglas Galasko\textsuperscript{d}, Jose Luis Molinuevo\textsuperscript{e}, Stephen Salloway\textsuperscript{f}, Suzanne Schindler\textsuperscript{g}, Maria C. Carrillo\textsuperscript{h}, James A. Hendrix\textsuperscript{h,\,*}, April Ross\textsuperscript{h}, Judit Illes\textsuperscript{i}, Courtney Ramus\textsuperscript{i}, Sheila Fifer\textsuperscript{j}

Alzheimer’s & Dementia 14 (2018) 1505-1521
Appropriate CSF usage

1. Subjective cognitive impairment considered at risk of AD
2. Persistent, progressive, unexplained MCI
3. Symptoms suggestive of possible AD
4. MCI or dementia with age of onset < 65
5. Meeting core clinical criteria for AD with typical age of onset
6. Dominant behavioural presentation where AD is considered diagnostically
Inappropriate CSF usage

1. Asymptomatic with normal objective cognition and no clinical suspicion of AD
2. Cognitively unimpaired but with positive family history
3. Cognitively unimpaired ApoE4 carriers
4. Subjective cognitive impairment not considered at risk of AD
5. Autosomal AD mutation carriers with or without symptoms
6. To determine disease severity in people with AD already diagnosed
Future biomarkers
CSF biomarkers
limitations
Limitations

Scalability
Cost
Infrastructural requirements
Patient acceptability
Assay variability
  between-batch
  between-lab
  ELISA vs Luminex
Results interpretation
  age-related norms
  diurnal variation
  categorical (normal/abnormal) vs continuous variable
Limitations

Scalability
Cost

**Infrastructural requirements**

Patient acceptability

Assay variability
  - between-batch
  - between-lab
  - ELISA vs Luminex

Results interpretation
  - age-related norms
  - diurnal variation
  - categorical (normal/abnormal) vs continuous variable
Infrastructural requirements for LP

Staff training
Facilities for aseptic prep
Day case unit with access to resuscitation services

Sample handling
  centrifugation
  -80° freezer
  courier to London labs for ELISA/Luminex assay
Limitations

Scalability
Cost
Infrastructural requirements
**Patient acceptability**
Assay variability
  - between-batch
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  - ELISA vs Luminex
Results interpretation
  - age-related norms
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Detecting and diagnosing Alzheimer’s disease

Enhancing our understanding of public attitudes to improving early detection and diagnosis

December 2019

MSD | Dementia Access Taskforce | Alzheimer’s Research UK
Diagnostic test acceptability

Cerebrospinal fluid (CSF) sampling

40% of those surveyed were fairly/very willing to have an CSF

10% didn't know

50% were not at all/not very willing

Figures taken from Populus Survey, 2019

Cognitive test

82% of those surveyed were fairly/very willing to have a cognitive test

6% didn't know

12% were not at all/not very willing

Brain imaging

75% of those surveyed were fairly/very willing to have an MRI/PET scan

7% didn't know

18% were not at all/not very willing

Blood test

81% of those surveyed were fairly/very willing to have a blood test

6% didn't know

13% were not at all/not very willing
Summary

• CSF biomarkers reflect AD pathology
• Added prognostic value
• Useful in research settings
  – stratification for trials
• Ongoing work re:
  – role in clinical practice
  – lab variability
  – test availability