Cutting Edge lecture

‘Biomarkers for the diagnosis and monitoring of progression in Alzheimer’s disease’

Dr Ivan Koychev, University of Oxford
Introduction

Alzheimer's disease (AD) is the most common type of neurodegenerative dementia, accounting for 50-70% of prevalent neurodegenerative dementia cases (Winblad et al., 2016). AD causes a progressive decline in cognitive function with the most typical initial symptom being short-term memory impairment.

AD neuropathology is characterised by:

- **neuronal loss** in specific brain regions – notably the medial temporal lobe structures and the temporo-parietal association cortices
- intraneuronal **neurofibrillary tangles** composed of aggregated and often truncated and hyperphosphorylated **tau protein**; and
- extracellular neuritic **plaques**, consisting of deposits of **β-amyloid** peptides (Blennow et al., 2006)


Introduction

Currently, clinical diagnosis of AD relies largely on documenting cognitive decline. This can be supplemented by additional parameters assessed through clinical investigations, such as blood tests and structural imaging. At the point of diagnosis, the disease has already caused severe brain damage.

Increasingly, and particularly with the prospect of disease modification, there has been a shift towards the use of biomarkers (Dubois et al., 2014) to diagnose AD earlier (pre-dementia stages) and with more specificity. Besides the clinical benefits of early and specific diagnosis, the use of biomarkers will enable the monitoring of disease progression and facilitate clinical trials of novel candidate drugs.

Intended Learning Outcomes

By completing this module, you will:

✓ **Review** up-to-date understanding of the role of neurofibrillary tangles and amyloid plaques in AD pathology
✓ **Understand** the terms *Alzheimer’s Disease* and *Alzheimer’s Dementia*
✓ **Identify** potential biomarkers for AD diagnosis and progression in four main areas:
  ✓ Cognition
  ✓ Neurodegeneration
  ✓ Amyloid
  ✓ Tau
✓ **Recognise** currently available biomarkers for AD and **categorise** potential future biomarkers as ‘*near future*’ and ‘*distant future*’
Biomarkers for the diagnosis and monitoring of progression in Alzheimer’s disease

The Gatsby/Wellcome Neuroscience Spring Conference

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Disclosures

• NIHR trainee
• MRC grants: Deep and Frequent Phenotyping study, Dementias Platform UK, MRC-NIH Partnership in Neurodegeneration
• Academy of Medical Sciences Clinical Lecturer Starter Grant
• Oxford Alzheimer’s Research UK
• Oxford University Clinical Graduate School
• Advisory Board Mantrah Ltd
Microscopic pathology

a

Amyloid plaque

b

Amyloid plaque

Stage A

Stage B

Stage C

Neurofibrillary tangle

Stage I and II

Stage III and IV

Stage V and VI

Severity

Nature Reviews | Disease Primers
Biomarker temporal sequence

Jack et al. 2013 Lancet Neurology
Alzheimer’s disease risk factors

Livingston et al. 2017 Lancet
APOE4 carriership effect

Jensen et al. JAMA 2015
Alzheimer’s disease vs dementia

- Clinical criteria: Probable Alzheimer’s dementia
  Dementia + progressive + >2 cognitive domains

- Amyloid/Tau/Neurodegeneration framework: Alzheimer’s disease

  - $A+$: CSF $\beta$-Amyloid <1025 pg/ml
  - $T+$: CSF $\tau$-Tau >24 pg/ml
  - $N+$: Schelten’s score = 1 (<65 yrs)
    Schelten’s score = 1.5 (65-75 yrs)
    Schelten’s score = 2 (>75 yrs)

- Emergent Alzheimer’s disease: Rapid amyloid/tau accumulation

<table>
<thead>
<tr>
<th>ATN profiles</th>
<th>Biomarker category</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A^{-}T^{-}(N^{-})$</td>
<td>No pathology</td>
</tr>
<tr>
<td>$A^{+}T^{-}(N^{-})$</td>
<td>AD pathologic change</td>
</tr>
<tr>
<td>$A^{+}T^{-}(N^{+})$</td>
<td>AD pathologic change</td>
</tr>
<tr>
<td>$A^{+}T^{+}(N^{-})$</td>
<td>AD pathology</td>
</tr>
<tr>
<td>$A^{-}T^{+}(N^{+})$</td>
<td>Non-AD pathology</td>
</tr>
<tr>
<td>$A^{-}T^{+}(N^{-})$</td>
<td>Non-AD pathology</td>
</tr>
</tbody>
</table>
Biomarkers

• Main biomarkers
  • Cognition
  • Neurodegeneration
  • Amyloid
  • Tau

• Experimental biomarkers: ADLs, sleep, synaptic function

• Availability
  • Current
  • Near future
  • Distant future
Cognition: Current
Cognition: Current/near future

Acquisition

Recall
Cognition: Near future

Lancaster, Koychev et al. In press
Cognition: Near future

Lancaster, Koychev et al. In press
Cognition: (Not too) distant future

• Personal digital technology interaction
  • Adapted browsers
    • Typing speed
    • Speed of reading
  • Smartphone
    • Find correct words when texting
    • Time to find contact
    • Speech analysis (machine learning)
  • Internet of things
    • Pattern of use of technology around the house (machine learning)
Cognition: (Not too) distant future

Trigoni, Koychev et al. In prep
Neurodegeneration: Current

MRI on coronal plane of the temporal lobe

- Hippocampus or Ammon horn
- Choroidal fissure
- Sylvian fissure
- Sup. temporal gyr
- Sup. temporal sulcus
- Middle temp. gyr
- Inf. temporal sulcus
- Inferior temporal gyrus
  - Occipito temporal sulcus
- Para hippocampal
  - posteriory temporal limpad
- Collateral sulcus
- Fusiform gyrus
- Occipito temporal sulcus

With a blue caption:
- gyrus
With a red caption:
- sulcus
# Neurodegeneration: Current

## MTA visual rating scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Width of choroid fissure</th>
<th>Width of temporal horn</th>
<th>Height of hippocampal formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>↑</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>3</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>4</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>↓↓↓</td>
</tr>
</tbody>
</table>
Neurodegeneration: Current

AD: posterior cingulate gyrus and parietal cortices extending to temporal

FTD: frontal and temporal cortices

LBD: occipital + parietal

Neurodegeneration: Near future
Neurodegeneration: Plasma NfL

Mattsson et al.  
JAMA Neurol. 2019
## Amyloid and tau: Current Diagnostic groups Biomarker AUC (95% CI) Specificity (%)*

<table>
<thead>
<tr>
<th>Diagnostic groups</th>
<th>Biomarker</th>
<th>AUC (95% CI)</th>
<th>Specificity (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD vs HC</td>
<td>AβX-42/X-40 ratio</td>
<td>0.95 (0.92–0.99)</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>Aβ1–42 (pg/mL)</td>
<td>0.93 (0.88–0.98)</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>T-tau/Aβ1–42 ratio</td>
<td>0.93 (0.89–0.97)</td>
<td>83%</td>
</tr>
<tr>
<td>AD vs DLB</td>
<td>AβX-42/X-40 ratio</td>
<td>0.73 (0.59–0.88)</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td>T-tau/Aβ1–42 ratio</td>
<td>0.77 (0.66–0.88)</td>
<td>40%</td>
</tr>
<tr>
<td>AD vs bvFTD</td>
<td>T-tau/Aβ1–42 ratio</td>
<td>0.89 (0.85–0.94)</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>AβX-42/X-40 ratio</td>
<td>0.86 (0.77–0.94)</td>
<td>85%</td>
</tr>
<tr>
<td>AD vs PNFA</td>
<td>T-tau/Aβ1–42 ratio</td>
<td>0.67 (0.54–0.80)</td>
<td>24%</td>
</tr>
</tbody>
</table>
Amyloid: Near future

Amyloid: Near future

Amyloid: Distant future

Nakamura et al. Nature 2018
Tau: Near future

Ossenkoppele et al. Brain 2016
Tau: Near future

A. Braak stages (post mortem)
- Transentorhinal (I/II)
- Limbic (III/IV)
- Neocortical (V/VI)

B. Tau tracer uptake (PET)
- $\text{Stage}_{\text{V/VI}} > \text{Stage}_0$
- $\text{Stage}_{\text{III/IV}} > \text{Stage}_{\text{V/VI}}$
- $\text{Stage}_{\text{V/VI}} > \text{Stage}_{\text{III/IV}}$

Schoell et al. Molecular and Cellular Neuroscience 2018
Tau: Near future

\[ *R = -0.56, p = 0.06 \]

Koychev et al. 2018 JAD
Tau: Distant future

Janelidze et al. Nature Medicine 2020
Tau: Distant future

Janelidze et al. Nature Medicine 2020
Tau: Distant future

Janelidze et al. Nature Medicine 2020
Experimental biomarkers
Experimental biomarkers: Sleep

Shokri-Kojori et al. PNAS 2018
Experimental biomarkers: Retinal imaging

Koronyo et al. JCI Insight. 2017
Experimental biomarkers: Synaptic function

Sami S et al. Brain. 2018
So what?

• Differential diagnosis
• Neurodegeneration prediction
• Preclinical diagnosis
  • Preclinical AD diagnosis -> ATN status
  • Emergent AD identification
• Preclinical disease tracking -> modification trials
Neurodegeneration prediction

La Joie et al. 2020 Science Translational Medicine
Emergent AD: Rapid accumulators

A

B

C

Koychev, Vaci et al. In press
Emergent AD: Switch-on time point

Figure 2

Koychev, Vaci et al. In press
Emergent AD: Switch-on time point

Koychev, Vaci et al. In press
## Summary

<table>
<thead>
<tr>
<th></th>
<th>Current</th>
<th>Near</th>
<th>Distant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognition</strong></td>
<td>Pen and paper Computerised</td>
<td>Smartphone cognitive tests</td>
<td>Passive monitoring</td>
</tr>
<tr>
<td></td>
<td>tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amyloid</strong></td>
<td>CSF</td>
<td>PET amyloid</td>
<td>Blood tests (Abeta42/40 + (P-tau181))</td>
</tr>
<tr>
<td><strong>Tau</strong></td>
<td>CSF</td>
<td>PET tau</td>
<td>Blood tests (P-tau181)</td>
</tr>
<tr>
<td><strong>Neurodegeneration</strong></td>
<td>CT/MRI</td>
<td>FDG PET</td>
<td>Blood tests (NfL)</td>
</tr>
</tbody>
</table>
## Potential use

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Differential diagnosis</th>
<th>Trial inclusion</th>
<th>Preclinical trial endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognition</strong></td>
<td>• Smartphone cognitive tests</td>
<td>• Pen and paper computerised tests</td>
<td>• Syndrome</td>
<td>• Smartphone cognitive tests</td>
</tr>
<tr>
<td></td>
<td>• Passive monitoring (Sleep)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amyloid</strong></td>
<td>• Blood tests (Abeta42/40)</td>
<td>• CSF</td>
<td>• PET amyloid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ophthalmology</td>
<td>• PET amyloid</td>
<td>• CSF</td>
<td></td>
</tr>
<tr>
<td><strong>Tau</strong></td>
<td>• Blood tests (P-tau181)</td>
<td>• CSF</td>
<td>• (PET tau)</td>
<td>• PET Tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PET tau</td>
<td></td>
<td>• Blood tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blood tests (P-tau181)</td>
<td></td>
<td>• (synaptic function)</td>
</tr>
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<td><strong>Neurodegeneration</strong></td>
<td>• Blood tests (NfL)</td>
<td>• CT/ MRI, FDG PET</td>
<td></td>
<td>• FDG PET</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blood tests (NfL)</td>
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</tr>
</tbody>
</table>
Thank you
Diagnosis and monitoring of progression in Alzheimer’s Disease (AD) is crucial to achieving high-quality clinical care. This, in turn, depends on the identification of reliable biomarkers and the development of appropriate methodologies for their measurement and testing.

Research is being driven by the realisation that the pathological process underlying AD begins up to 25—30 years before clinical symptoms appear. Consequently, AD should be thought of as a ‘life-course’ disease and prevention should begin much earlier than it has previously.

Passive, remote monitoring using digital technology (apps, wearables) is likely to be particularly useful for patient stratification, especially in identifying patients in the preclinical stage of dementia. Significantly, these methodologies offer the possibility to analyse memory function repeatedly and over much longer time periods (seven days or more) compared with testing in the clinic (15—20 minutes). Remote monitoring and analysis also overcomes difficulties of access to clinical services for patients living away from specialised centres.
New methodologies such as Tau-PET make it possible to determine a person’s disease status in terms of Braak staging, which previously was possible only post mortem. This offers real potential for the staging of AD, much like oncologists’ capacity for staging cancer.

Blood tests are likely to become much more common in the near future as disease-modifying therapies become available. Plasma biomarkers such as NF-L (neurofilament ‘light’ [low molecular weight neurofilament protein]), especially used in combination, may be valuable for differential diagnosis. Measuring these is relatively non-invasive (compared with CSF analysis or scans), and of low-cost (compared with PET or MRI). Plasma NF-L has now been strongly correlated with neurodegeneration.
For each of the following questions, choose the best answer from the options given. *Answers on the next slide.*

1. Approximately how many years before symptom onset does β-amyloid deposition in the brain begin?
   A) 2 years  
   B) 20 years  
   C) 5 years  
   D) 30 years

2. Neurofilaments are:
   A) Structural proteins found in the presynaptic membrane  
   B) Structural proteins found in the axon  
   C) Connected to ion channels in the axon terminal  
   D) Found in the extracellular space between neurons and glial cells

3. The ATN framework is based on the measurement of which three biomarkers?
   A) Amyloid/Tau/Neurofilament  
   B) Alzheimer’s/Tau/Neurodegeneration  
   C) Alzheimer’s/Time/Neurodegeneration  
   D) Amyloid/Tau/Neurodegeneration

4. Measuring the amyloid Aβ-42/-40 ratio in the CSF is based on the finding that as AD progresses:
   A) CSF Aβ-42 decreases while Aβ-40 remains high  
   B) CSF Aβ-42 remains high while Aβ-40 increases  
   C) CSF Aβ-42 decreases and Aβ-40 decreases  
   D) CSF Aβ-42 increases and Aβ-40 increases
# Self-assessment of learning

## Answers.

1. Approximately how many years before first symptoms does β-amyloid deposition in the brain begin?
   - A) 2 years
   - B) 20 years
   - C) 5 years
   - **D) 30 years**

2. Neurofilaments are:
   - A) Structural proteins found in the presynaptic membrane
   - **B) Structural proteins found in the axon**
   - C) Connected to ion channels in the axon terminal
   - D) Found in the extracellular space between neurons and glial cells

3. The ATN framework is based on the measurement of which three biomarkers?
   - A) Amyloid/Tau/Neurofilament
   - B) Alzheimer’s/Tau/Neurodegeneration
   - C) Alzheimer’s/Time/Neurodegeneration
   - **D) Amyloid/Tau/Neurodegeneration**

4. Measuring the amyloid Aβ-42/-40 ratio in the CSF is based on the finding that as AD progresses:
   - A) **CSF Aβ-42 decreases while Aβ-40 remains high**
   - B) CSF Aβ-42 remains high while Aβ-40 increases
   - C) CSF Aβ-42 decreases and Aβ-40 decreases
   - D) CSF Aβ-42 increases and Aβ-40 increases
Fifth Neuroscience Spring Conference
Translating neuroscience knowledge to clinical practice
London, March 13, 2020

Extension activities

Extend your learning by following one of these suggestions:

**WATCH** Dr Vanessa Raymont on the [Deep & Frequent Phenotyping](#) (DFP) study. More details [here](#).


**WRITE** a 750-word article on ‘Biomarkers in Alzheimer’s Disease’ and submit it to ‘Psynapse’, the RCPsych’s Neuroscience eNewsletter (visit [rcpsych.ac.uk/training/neuroscience-in-training/neuroscience-resources](#) for inspiration). Published articles will earn you a £50 discount on registration for the RCPsych 2021 Neuroscience Spring Conference, London, 26 March 2021. *Submit your article [here](#).*