Changing diagnostic criteria for AD - Impact on Clinical trials

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1) Consultancy:
   Affiris, Eli Lilly, Roche

2) Funding for my Institution:
   Pfizer, Roche
IWG-1 criteria (2007-2010)

First introduction of different AD clinical stages
- prodromal stage
- dementia stage

First introduction of different AD preclinical states
- asymptomatic at risk (biomarker positive)
- presymptomatic (mutation carriers)

First introduction of different forms of AD
- typical
- atypical

One disease: one set of criteria

AD: a clinico-biological entity
The conceptual shift

1984 NINCDS-ADRDA

Clinical pathological entity

ALZHEIMER’S DISEASE

MCI

Dementia

Probable/possible

Neuropathology

2007 IWG

Clinical biological entity

ALZHEIMER’S DISEASE

Typical / atypical

Biomarkers

CLINICAL

POST-MORTEM

CLINICAL

BIOLOGICAL
The different biomarkers of AD

**PATHOPHYSIOLOGICAL MARKERS**

- CSF Abeta and tau levels
- PET amyloid radio-ligand

**TOPOGRAPHICAL MARKERS**

- Amnestic syndrome of the hippocampal type
- Hippocampal atrophy (MRI)
- Cortical hypometabolism (FDG-PET)

**LESIONS of AD**

- nature (2 types: amyloid, tau)
- location

**LESIONS of AD**

- hippocampal atrophy (MRI)
- cortical hypometabolism (FDG-PET)
The 2 types of biomarkers (*LN*, 2014)

**Diagnostic markers**
- Pathophysiological markers
- Reflect in-vivo pathology (amyloid and tau changes)
- Are present at all stages of the disease
- Observable even in the asymptomatic state
- Might not be correlated with clinical severity
- Indicated for inclusion in protocols of clinical trials

**Progression markers**
- Topographical or downstream markers
- Poor disease specificity
- Indicate clinical severity (staging marker)
- Might not be present in early stages
- Quantify time to disease milestones
- Indicated for disease progression
A simplified algorithm is proposed:

In any condition and at any stage of the disease, the diagnosis of AD relies on the presence of a pathophysiological marker.

**Typical**
- Amnestic syndrome of the Hipp. type

**Atypical**
- Posterior cortical atrophy
- Logopenic variant
- Frontal variant

**Asymptomatic at risk**
- No AD phenotype (typical or atypical)

**Presymptomatic** (AD mutation)
- No AD phenotype (typical or atypical)

- CSF (low β1–42 and high T or P-tau)
  **OR**
- Amyloid PET (high retention of tracer)
IWG-2 criteria for typical AD, at any stage
For instance, for prodromal AD

CLINICO - BIOLOGICAL ENTITY

- Amnestic syndrome of the hippocampal type
- Isolated or associated with other cognitive or behavioral changes

- CSF (low β1–42 and high T or P-tau)
  OR
- Amyloid PET (+)
(3) NIA/AD diagnostic Criteria

The NIA/AA criteria acknowledge that:
- brain changes can occur long before dementia symptoms
- disease biomarkers might be useful for the diagnosis

3 recognized stages with 3 different diagnostic algorithms
- AD dementia stage (10 categories)
- MCI stage (4 categories)
- preclinical stage (3 categories)

2 types of MCI criteria:
- for clinical setting
- for research purposes that are based on the use of biomarkers:

<table>
<thead>
<tr>
<th>Cognition</th>
<th>Likelihood of AD</th>
<th>Biomarker Evidence</th>
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<tbody>
<tr>
<td>MCI</td>
<td>High likelihood</td>
<td>(+) amyloid-β biomarker AND (+) neuronal injury biomarker*</td>
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<td>MCI</td>
<td>Intermediate likelihood</td>
<td>(+) amyloid-β biomarker OR (+) neuronal injury biomarker*</td>
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<td>MCI</td>
<td>Uninformative situation</td>
<td>Biomarkers fall in ambiguous ranges, conflict, not obtained</td>
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<td>MCI</td>
<td>Unlikely due to AD</td>
<td>Demonstrated absence of AD-type molecular marker and possible presence of marker suggestive of non-AD disorder</td>
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« Early AD »: the right target

- This includes ‘Prodromal + Mild AD dementia’
- IWG-2 criteria with MMS ≥ 20

Advantages:
- Focus on early stage of AD
- One disease = One set of criteria
- Possibility for a secondary stratification
Who are they?

**Presymptomatic AD**
- with autosomal dominant monogenic AD mutation:
  - they will develop AD

**Asymptomatic at risk for AD (AR-AD)**
- with a positive pathological marker (brain or CSF):
  - they will or will not develop AD

_Dubois et al, Lancet Neurology, 2010_
IWG-2 criteria for asymptomatic at risk

Absence of specific clinical phenotype of AD (both are required):
- Absence of amnestic syndrome of the hippocampal type
- Absence of any clinical phenotype of atypical AD

- CSF (low β1–42 and high T or P-tau)
  OR
- Amyloid PET (+)
Should we treat subjects at preclinical states?

- **Drugs**
  - Yes, if drugs decrease AD brain lesions
  - Yes, if drugs have no side effects in the long term

- **Design**
  - Yes, if we know how to assess the clinical efficacy at preclinical stages

- **Subjects**
  - Yes, if we can ascertain that they all will further develop Alzheimer’s disease
Unresolved Issues about AR-AD

1) Will they all convert to AD? Ethical issues:
   • What should we disclose about their status and their risk?
   • Can we treat someone against a disease that he/she will never develop?

2) When will they convert to AD? Therapeutic issues:
   • Duration of the study?

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A need to better know the natural history of AD
A need to identify markers of a further conversion
IWG-2 criteria for presymptomatic AD

Absence of specific clinical phenotype of AD (both are required):
- Absence of amnestic syndrome of the hippocampal type
- Absence of any clinical phenotype of atypical AD

Proven AD autosomal dominant mutation for AD
Added-value of the IWG-2 criteria

- They focus on the **entire continuum** of AD including the preclinical states;
- They utilize a **single diagnostic framework** for the entire range of clinical severity;
- They integrate **pathophysiological** biomarkers into all phases of the diagnostic approach to improve on the diagnostic specificity;
- AD diagnosis is now based **at least** on the presence of brain amyloidosis;
- They integrate causative **mutations** into diagnosis;
- They are **simple** to apply;
- They can be used for inclusion of patients with « early AD », an important target for clinical trials.
Limitations

• The willingness of individuals to undergo lumbar puncture
• The criteria mainly apply for research, memory clinics and expert centers
• There are ethical and practical concerns about disclosure of biomarker status in asymptomatic or very early symptomatic individuals
• Norms are needed for biomarkers
• Norms are needed for episodic memory tests that can be applied for a wide range of age, education, culture
• This requires a coordinated international effort
We gratefully acknowledge the IWG participants