„The added value of the IWG-2 diagnostic criteria for Alzheimer’s’ disease”

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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

Clinical biological entity

2007 IWG

alzheimer’s disease

MCI
dementia
probable/possible

neuropathology

CLINICAL

POST-MORTEM

alzheimer’s disease

typical / atypical

biomarkers

CLINICAL

BIOLOGICAL

The conceptual shift within the study of Alzheimer's disease highlights a significant change in understanding the disease from a clinical pathological perspective to a clinical biological perspective. The 1984 NINCDS-ADRDA criteria provided a framework for clinical diagnosis, whereas the 2007 IWG criteria introduced a more comprehensive approach that integrates clinical, biological, and pathological aspects, including the consideration of typical and atypical biomarkers.
The different biomarkers of AD

**PATHOPHYSIOLOGICAL MARKERS**

- CSF Abeta and tau levels
- Amyloid PET
- Tau PET

**TOPOGRAPHICAL MARKERS**

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

**LESIONS of AD**

- **nature**
  - 2 types: amyloid, tau

- **location**
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

*Lancet Neurology, June 2014*
IWG-2 criteria for typical AD, at any stage

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

CLINICO - BIOLOGICAL ENTITY

- 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>
</tr>
</thead>
<tbody>
<tr>
<td>MCI</td>
<td>High likelihood</td>
<td>(+) amyloid-β biomarker <strong>AND</strong> (+) neuronal injury biomarker*</td>
</tr>
<tr>
<td>MCI</td>
<td>Intermediate likelihood</td>
<td>(+) amyloid-β biomarker <strong>OR</strong> (+) neuronal injury biomarker*</td>
</tr>
<tr>
<td>MCI</td>
<td>Uninformative situation</td>
<td>Biomarkers fall in ambiguous ranges, conflict, not obtained</td>
</tr>
<tr>
<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>
</tr>
</tbody>
</table>
Prodromal versus MCI due to AD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IWG-2</th>
<th>NIA/AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiological markers only</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>At least, amyloid marker necessary</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Specific clinical phenotype required</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Integration within a continuum</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Different levels of likelihood</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Only clinical</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>
« 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_
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 \(\beta_1-42\) and high T or P-tau)

**OR**

**Amyloid PET** (high retention of tracer)
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)
• Amyloid PET (+)
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.
AD: starts with the first specific symptoms and encompasses both the prodromal and dementia phases

**AD dementia:** phase of AD with an impact on ADL

**Prodromal AD:** the early symptomatic, predementia phase of AD

Typical AD: common clinical phenotype of AD, characterized by an early amnestic syndrome of the hippocampal type

**Atypical AD:** less common but well characterized clinical phenotypes: logopenic aphasia, posterior cortical atrophy, frontal variant of AD.

The diagnosis of AD needs in vivo evidence of pathophysiological markers

Mixed AD: patients who fulfill the criteria for AD with clinical and biomarkers evidence of other co-morbid disorders

*(Dubois et al, Lancet Neurology 2010)*
Preclinical stages of AD

**Asymptomatic at risk:** cognitively normal individuals with in vivo pathophysiological biomarkers of AD

**Presymptomatic AD:** cognitively normal individuals with a proven autosomal dominant mutation

**Alzheimer’s pathology:** neurobiological changes responsible for AD

**Pathophysiological markers:** in vivo biological changes that reflect the underlying AD pathology (CSF Abeta and tau; PET-amyloid).

They are markers of diagnosis, more targeted at identifying AD.

**Topographical biomarkers:** downstream markers of neurodegeneration: can be structural (atrophy/MRI) or metabolic (hypometabolism/FDG-PET).

They are markers of progression, more targeted at assessing changes over time and predicting outcomes.
What’s next?

• The preclinical states of AD
AD = a continuum with different stages

......compensated state..........<........... decompensated state.................>

STAGE

preclinical       prodromal       dementia

BIOMARKER
of Alzheimer pathology

☐ positive        ☐ positive        ☐ positive

COGNITION

☐ normal          ☐ Amnestic S of the H. type ☐ Cognitive/behavioral chges

☐ Impact on ADL
NIA-AA: Preclinical AD

Stage 1
Asymptomatic amyloidosis
- High PET amyloid tracer retention
- Low CSF Aβ1-42

Stage 2
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

MCI $\rightarrow$ AD dementia
PART is part of Alzheimer disease

Charles Duyckaerts · Heiko Braak · Jean-Pierre Brion · Luc Buée · Kelly Del Tredici · Michel Goedert · Glenda Halliday · Manuela Neumann · Maria Grazia Spillantini · Markus Tolsny · Toshiki Uchihara

« Entorhinal-hippocampal tau pathology is an invariant feature of AD and is always associated with its development ».
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?

→ to better know the natural history of AD
→ identify predictive markers of a further conversion
→ identify the risk/preventive factors of a clinical disease
The risk for AD - Hypothetical model

Risk for AD

ApoE 4, age, genetic factors, circulating agents, comorbidity…
Cognitive/brain reserve

dynamic process of conversion

clinical threshold

Clinical AD

BM (+)
BM (-)
We gratefully acknowledge the IWG participants