Criteria for AD Dementia- Revised

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Consultant: Previous- Wyeth, GSK
Present-Merck DSMB
Progression of Alzheimer’s Disease

- Normal
- MCI due to AD
- AD Dementia
Preclinical Workgroup

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Sponsored by NIA and Alzheimer’s Association
Concerns with the NINCDS/ADRDA Criteria

1) The concept of the **continuum** of AD
   Pre-symptomatic – MCI - AD Dementia

2) The implication that memory impairment is always the primary cognitive deficit in all patients with AD dementia

3) Lack of discussion of other dementing conditions

4) No discussion of biomarkers (MR imaging, PET imaging, CSF assays – did not exist)

McKhann et al., Neurology, 1984
Goals of Committee

- Review and revise previous criteria (NINCDS/ADRDA)
- Core set of clinical criteria with wide application (community clinicians, academic researchers, industry)
- Enhancement of certainty of diagnosis
  - Use of Biomarkers
Additional Concerns

• Proposed age cutoffs for the diagnosis of AD dementia
• Need for adaptation for culture and language differences
• Implied requirement for neuropsychology testing, which may not be available in many clinical settings.
• Possible AD dementia category, included a group of patients who would now be diagnosed as “mild cognitive impairment.”
• Recognition of patients with mixed pathology (vascular disease and Lewy Body disease)
Overview

• Describe clinical and cognitive criteria for AD dementia

• Outline criteria for AD dementia
  – Pathologically Proven, Probable, Possible

• Describe framework for approach to biomarkers
Criteria for all-cause Dementia

Dementia is characterized by the impairment of at least two of the following:
- Impaired learning and retention of new information
- Impaired reasoning and handling of complex tasks
- Impaired spatial and visuo-construction abilities
- Impaired language functions

The cognitive impairment interferes with work or usual social activities.
The cognitive impairment represents a decline from prior levels of functioning.
Not explained by delirium nor major psychiatric disorder.
Criteria for the Diagnosis of AD Dementia
Clinical and Cognitive Criteria

- **Insidious Onset**: Cognitive symptoms have a gradual onset over many months-years (onset not sudden over hours or days)

- **Gradual Progression**: Clear-cut history of worsening of cognition by report or observation
Criteria for the Diagnosis of AD Dementia
Clinical and Cognitive Criteria

• **Deficits are evident on history or examination**
  – Significant impairment in two or more cognitive domains
  – Range of cognitive presentations
  – Impairment in social and occupational function
Amnestic Presentation

• Most common presentation of AD dementia
• The deficits should include impairment in learning and recall of recently learned information.
• There should also, over time, be evidence of cognitive dysfunction in other cognitive domains.
Non-amnestic Presentation (1)

• Language dysfunction: Most prominent deficits are in word-finding, but dysfunction in other cognitive domains should ultimately be present

• Often confused with forms of FTLD (Primary Progressive Aphasia and Semantic Dementia)
Non-amnestic Presentation (2)

• Visuospatial dysfunction: **Most prominent deficits are in spatial cognition – e.g., object agnosia, impaired face recognition. Deficits in other cognitive domains should ultimately be present.**
Non-amnestic Presentation (3)

• Executive dysfunction: most prominent deficits are in impaired reasoning, judgment and problem solving. Deficits in other cognitive domains should ultimately be present
Levels of Certainty
Original Criteria

• **Definite:** Autopsy proven
• **Probable:**
• **Possible:**
Levels of Certainty
New Criteria

• **Pathologically proven AD dementia**

• **Probable AD dementia**
  - Enhanced probability
    » Documented decline
    » Mutation carrier
    » Biomarker positive

• **Possible AD dementia**
  » Atypical course
  » Biomarkers negative
  » Mixed presentation
Pathologically proven AD Dementia

- Meets clinical and cognitive criteria for probable AD dementia during life
- Proven AD by pathological examination
- Pathologically characterized AD, without corresponding clinical criteria would not be considered “Pathologically proved AD Dementia”
Probable AD Dementia

• Meets clinical and cognitive criteria for AD dementia
• Without evidence of any alternative diagnoses
Probable AD Dementia
Enhanced Probability

• Documented longitudinal decline

• AD genetic mutation carrier

• Positive evidence from biomarkers
Probable AD Dementia
Enhanced Probability (1)

- Documented Decline: Longitudinal assessment documenting decline in cognition
  » Standard neuropsychological testing
  » Brief office assessment
AD Genetic Mutation Carrier

- Meets clinical and cognitive criteria for AD Dementia
- Has a proven AD autosomal dominant genetic mutation (PSEN1, PSEN2, APP).
Probable AD Dementia
Enhanced Probability (2)

- Examination of Biomarkers
  » Biomarkers that increase certainty that AD is underlying pathology
  » Biomarkers that are indication of progression of AD dementia
Biomarkers

• **Molecular Pathology of AD Dementia**
  – CSF Abeta 42
  – CSF tau/ phospho tau
  – Amyloid Imaging

• **Downstream Measures of Structural Change**
  – Hippocampal Volume
  – Medial Temporal Lobe Atrophy

• **Downstream Measures of Functional Change**
  – FDG PET
  – SPECT Perfusion
Biomarkers obtained and Negative:

- In many cases, imaging and CSF biomarker results will be clearly normal or abnormal.
- In some cases, ambiguous results will be obtained and it may be able to further classify some of these as positive or negative with more sophisticated quantitative and objective image analysis methods.
- CSF findings rely completely on a quantitative readout with comparison to norms. These quantitative techniques are, and will continue to be in evolution for some time.
- Therefore practical use of biomarkers must follow local best-practice guidelines, until standardization has been fully accomplished.
Hypothetical Model of Biomarkers

Abnormal

Normal

Pre-symptomatic  EMCI  LMCI  Dementia

Time

CSF Aβ42  Amyloid imaging  FDG PET  MRI hippocampal volume  CSF Tau  Cognitive performance  Function (ADL)

Jack et al., 2010
Biomarkers to Enhance Diagnosis

• Has one or more of the following supporting biomarkers
  • low CSF Aβ42, elevated CSF tau or phospho tau ratio
  • positive amyloid PET imaging
  • decreased FDG uptake on PET in temporoparietal cortex
  • Disproportionate atrophy on structural MR in medial temporal (esp. hippocampus), basal and lateral temporal lobe, and medial parietal isocortex.
Possible AD Dementia

- **Atypical Course**: Evidence for progression is lacking BUT patient meets other clinical and cognitive criteria for AD dementia

- **Mixed Presentation**: Patient has evidence of other concomitant disorders (cerebrovascular disease, DLB)

- **Biomarker Negative**: Patient meets clinical and cognitive criteria for AD dementia BUT biomarker measurements have been done, and are negative
Mixed Presentation

• Meets clinical and cognitive criteria for AD dementia but there is evidence of concomitant cerebrovascular disease, this would mean that there is >1 lacunar infarct, or a single large infarct or extensive, severe white matter hyperintensity changes.

• Evidence for some features of Dementia with Lewy Bodies that do not achieve a level of a diagnosis of probable DLB.
NOT AD Dementia

- Does not meet clinical criteria for AD dementia

  OR

- Has sufficient evidence for an alternative diagnosis such as HIV, Huntington’s disease, or others that rarely, if ever, overlap with AD
Other Potential Disorders

- Frontotemporal lobar degeneration (FTD, SD, PPA)
- Corticobasal syndrome
- Creutzfeld Jakob disease (CJD)
- Others: HIV Disease, effects of alcohol or drug usage, delirium, etc
Issues for Neuropathologists

• Concept of the continuum of Alzheimer’s disease
• Pathology of earlier stages of disease
• Correlation between biomarkers and pathology
• Identification of neuronal loss
• Mixed dementias
  – Overlap with vascular disease
Suggestion to neuropathologists

• Have a meeting to review issues and criteria
• Perhaps with representation from other committees
Progression of Alzheimer’s Disease

Cognitive Function

Normal

MCI due to AD

AD Dementia

Disease Progression