Introduction

In the fall of 1983, a group was convened to establish and to describe the clinical diagnosis of Alzheimer’s disease (AD). The group convened subgroups which addressed issues of medical history, clinical examination, neuropsychological testing, and laboratory assessments and then produced an integrated report, published in July 1984. The criteria in this report commonly referred to as the NINCDS-ADRDA criteria, have been quite successful, surviving for over 25 years. These criteria have been reliable for the diagnosis of probable AD, with a sensitivity of 80% and specificity of 70%. They have been widely used in clinical trials and clinical research.

However, now 26 years later, these criteria have some shortcomings that need to be addressed. Some relate to lack of knowledge at the time of the development of the original criteria. Others relate to the vast expansion of our knowledge of the biology of AD. Some of the shortcomings include:

1) Lack of distinguishing features of other dementing conditions that occur in a similarly aged population, but were not fully recognized 25 years ago
2) No inclusion of results of MR imaging, PET imaging and CSF assays (that we will refer to subsequently as biomarkers)
3) The implication that memory impairment is always the primary cognitive deficit in all patients with AD dementia
4) Lack of information about genetics of AD dementia.

There are other items included in the original criteria which proved to be ill-suited for use and should be reconsidered, which include:
1) Proposed age cutoffs for the diagnosis of AD dementia
2) Implied requirement for neuropsychological testing, which may not be available in many clinical settings.
3) Extreme heterogeneity of the “Possible” AD dementia category, including a group of patients who would now be diagnosed as “Mild cognitive impairment.”

The charge to our committee was to focus on the criteria for AD Dementia—that is dementia secondary to the pathophysiology of Alzheimer’s disease. It is our intention to first review the NINDS-ADRSA criteria and to update them, using more modern innovations in clinical, imaging, and laboratory assessment. We will first propose 1) Criteria for all-cause dementia and, 2) Criteria for AD dementia. These revised criteria must be flexible enough to be used by both general health care providers without access to neuropsychological testing, advanced imaging and CSF measures, as well as specialized investigators involved in research or in clinical trial studies who will have these measures available.

I. Criteria for all-cause Dementia
Dementia is diagnosed when there are cognitive and behavioral symptoms that:

- Interfering with work or usual social activities; and
- Represent a decline from prior levels of functioning and performing; and
- Are not explained by delirium nor major psychiatric disorder;
- Cognitive impairment is detected and diagnosed through a combination of history-taking from the patient, a knowledgeable informant and an objective cognitive assessment, either a “bedside” mental status examination or neuropsychological testing and involves at least two of the following domains:
  - Impaired ability to acquire and remember new information – symptoms: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route
  - Impaired reasoning and handling of complex tasks, poor judgment - symptoms: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
  - Impaired visual spatial and abilities - symptoms: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements or orient clothing to the body.
  - Impaired language functions (speaking, reading, writing) - symptoms: difficulty thinking of common words while speaking, hesitations; speech, spelling and writing errors
  - Changes in personality/usual character impaired motivation, initiative - Symptoms: increasing apathy, loss of drive; social withdrawal, decreased interest in previous activities.
II. Criteria for the Diagnosis of AD Dementia

- Insidious onset. Symptoms have a gradual onset over months to years, and the onset was not sudden over hours or days; and
- Clear-cut history of worsening of cognition by report or observation; and
- Cognitive deficits are evident on history and examination in one of the two categories:
  1. Amnestic presentation: The most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in other cognitive domains as defined above.
  2. Non-amnestic presentations:
     - Language presentation: The most prominent deficits are in word-finding, but dysfunction in other cognitive domains should be present.
     - Visual presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia and alexia. Deficits in other cognitive domains should be present.
     - Executive dysfunction: the most prominent deficits are in impaired reasoning, judgment and problem solving. Deficits in other cognitive domains should be present.

With this background we propose the following characterization for AD Dementia

1. Pathologically proved AD Dementia
   1. Meets clinical and cognitive criteria for probable AD dementia during life
   2. Proven AD by pathological examination

2. Clinical AD Dementia – Degrees of Certainty

We propose to maintain the “Probable” and “Possible” gradation of the 1984 criteria and add qualifiers to each:

A. Probable AD Dementia. Meets clinical and cognitive criteria for AD dementia given above under (II), AND without evidence of any alternative diagnoses, in particular, no significant cerebrovascular disease (See Footnote 1)

In persons who meet the basic criteria for probable AD dementia, the diagnosis of probable AD dementia can be enhanced by one of these 3 features that increase certainty:

1) **Documented Decline**: Has evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either brief
mental status examinations or formal neuropsychological evaluation (see Footnote 2).

OR

2) **Biomarker Positive:**
   Has one or more of the following supporting biomarkers (see Footnote 3):
   1. low CSF Aβ42, elevated CSF tau or phospho tau
   2. positive amyloid PET imaging
   3. decreased FDG uptake on PET in temporoparietal cortex
   4. Disproportionate atrophy on structural MR in medial temporal (esp. hippocampus), basal and lateral temporal lobe, and medial parietal isocortex.

OR

3) **Mutation Carrier:**
   Meets clinical and cognitive criteria for AD Dementia and has a proven AD autosomal dominant genetic mutation (PSEN1, PSEN2, APP).

B. Possible AD Dementia.

1) **Atypical Course:**
   Evidence for progressive decline is lacking or uncertain but meets other clinical and cognitive criteria for AD dementia

OR

2) **Biomarkers obtained and Negative:**
   Meets clinical and cognitive criteria for AD dementia but Biomarkers (CSF, structural or functional brain imaging) do not support the diagnosis (see Footnote 3).

OR

3) **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; or evidence for some features of Dementia with
Lewy Bodies that do not achieve a level of a diagnosis of probable DLB.

C. NOT AD.

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

Footnote 1: No significant cerebrovascular disease; <2 lacunar infarcts, no large vessel infarcts, and extensive, severe white matter hyperintensity changes

Footnote 2: Standard neuropsychological testing by a qualified neuropsychologist showing a significant decline (defined by statistically meaningful/reliable change in test scores) in a pattern of domains and at a rate consistent with AD-related change. Alternatively, clear-cut decline on a standardized bedside mental status examination could provide sufficient evidence for documented decline, provided the amount of decline meets local standards for clinically relevant decline.

Footnote 3: Biomarkers: low CSF Abeta42, elevated CSF tau or phospho tau; positive amyloid PET imaging; decreased FDG uptake on PET in temporo-parietal cortex; disproportionate atrophy on structural MR in medial temporal (esp. hippocampus), basal and lateral temporal lobe, and medial parietal isocortex. In many cases, imaging and CSF biomarker results will be clearly normal or abnormal. In these cases, a qualitative “read” of an imaging test will be able to accurately identify “positive” findings. In some cases, ambiguous results will be obtained and it may be possible 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. The priority of one biomarker over another in AD dementia has not been established, and further studies are needed. Therefore practical use of biomarkers must follow local best-practice guidelines, until standardization has been fully accomplished.