A New Concept and New Criteria for Alzheimer's Disease

a report by

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The diagnosis of Alzheimer's disease (AD) is a two-step process. First, a dementia syndrome, which is defined by impact on social functions or activities of daily living (ADL), is diagnosed. As a consequence, ADL impairment has become the threshold for the diagnosis of dementia beyond the identification of a cognitive abnormality. The second step consists of the exclusion of the aetiologies of a different dementia syndrome using paraclinical investigations, including neuroimaging and biological tests. AD, therefore, is mainly described in exclusionary terms, with investigations being used to identify other causes of dementia – vascular, tumoral and systemic.

This two-step procedure, which relies on the *Diagnostic and Statistic Manual of Mental Disorders IV Text Revision* (DSM-IV-TR) and the National Institute of Neurological and Communication Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, should be revised on the basis of several arguments. First, the criteria do not take into account the unprecedented growth of scientific knowledge concerning the existence of reliable biomarkers of AD that are now available through structural magnetic resonance imaging (MRI), molecular neuroimaging and cerebrospinal fluid analyses. Nor do they take into account the AD phenotype, which presents in most cases as a progressive amnestic dementia related to other Alzheimer's-related changes that involve the medial temporal structures early in the course of disease. Furthermore, the episodic memory disorders of AD correlate well with a distribution of neurofibrillary tangles within the medial temporal lobe (MTL) and with the demonstration by MRI of volumetric loss of the hippocampus, the structure known to be critical for episodic memory.

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In addition, recently developed disease-modifying therapies require early intervention at the prodromal stage before full-blown dementia. At the moment, the prodromal stage of AD is included under the heterogeneous term mild cognitive impairment (MCI). This heterogeneity may have contributed to the negative outcomes of clinical trials in which none of the drugs was successful in delaying the time to diagnosis of AD. It may be assumed that the heterogeneity of MCI has diluted the potential for a significant treatment effect, particularly considering that AD is already at work on the brain long before the onset of clinical dementia. However, it is possible to recognise this pre-dementia stage of AD by adopting a multidimensional approach, identifying:

- a specific amnestic disorder of the hippocampal type;
- the atrophy of medial temporal structures – specifically the hippocampus; and
- the specific profile of cerebrospinal fluid biomarkers or of metabolic neuroimaging changes.

An international working group was convened to discuss the opportunity to develop a diagnostic framework for AD that would include the prodromal stages. At the end of this consensus meeting it was concluded that it was possible to recognise AD at the prodromal, pre-dementia stage with the use of specific memory tests, biomarkers and neuroimaging investigations. There was no longer a reason to limit the diagnosis of AD to patients who reached the threshold of full-blown dementia. Accordingly, it was decided that new criteria be proposed that would apply both in the early stages and across the full spectrum of the illness.

Proposed Diagnostic Criteria for Probable Alzheimer's Disease

The framework addresses the presentations that are typical of AD. It excludes atypical presentations – primary progressive aphasia and visuospatial dysfunction – although it has been demonstrated that these atypical phenotypes can be associated with *post mortem* AD histological changes. To meet criteria for probable AD, an affected individual must fulfil the core clinical criterion (criterion A) and at least one of the supportive biomarker criteria (see *Table 1*).

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To satisfy criterion A, memory symptoms must start gradually and show progressive decline over at least six months. Particular attention should be paid to intra-individual decline, which improves the identification of those individuals with prodromal AD. The proposed criteria emphasise the specificity of memory changes of AD and the need to use specific memory tests. It is noteworthy that most of the current memory tests do not record whether items to be recalled have been truly registered. Effective encoding of information should be controlled in order to exclude memory deficit related to anxiety, depression, frontal dysfunction or any other functional disorder. In the same way, identification of AD can be improved by using semantic cueing that facilitates the retrieval of stored information in aged healthy people or in patients with subcorticofrontal dysfunction. Reduced benefit of cueing at recall reliably identifies prodromal AD. Episodic memory impairment is proposed as a core feature of AD. It can be isolated or associated with other cognitive changes at the onset of AD or as AD advances. As AD advances, these changes become notable and can involve several domains – executive function, language, praxis, complex visual processing and gnosis. The emergence of neuropsychiatric symptoms, including apathy or delusions, also constitutes a clinical marker of the disease. However, even in these more advanced cases there should be evidence of an early and previous episodic memory deficit as a mandatory requirement for the diagnosis of AD.

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The strength of these proposed research criteria rests in the introduction of neurobiological measures to the clinically based criteria. In previous criteria, the biological investigations were mainly used for excluding other causes of dementia. For example, in the NINCDS-ADRDA guidelines, cerebrospinal fluid (CSF) examination was recommended as an exclusion procedure for non-AD dementia due to inflammatory disease, vasculitis or demyelination. Since then, there has been a lot of evidence that abnormal biomarkers among structural neuroimaging with MRI, molecular neuroimaging with positron emission tomography (PET) or single photon emission computed tomography (SPECT) and CSF analysis of amyloid beta or tau proteins can be useful for the identification of AD. The criteria stipulate that there must be at least one abnormal biomarker in addition to the core diagnostic criterion. In the absence of validation studies, there is no possibility, at this time, of assigning differential weightings to the supportive features or recommending combinations of features or, alternatively, requiring the presence of all of the features. As new evidence accrues on biological markers for AD, especially those detecting AD-pathology-specific markers such as amyloid imaging, the weighting of the supportive features may change. We recognise that these criteria represent a cultural shift requiring more biologically focused work-up than previous approaches. However, this seems to be the best way to integrate the advances into the clinical arena. When effective disease-modifying medications are available, the argument for such biologically based studies will be even more compelling.

Validation studies are required because it is assumed that the proposed diagnostic criteria indicate the presence of the neurodegenerative process of AD. In addition, we recognise that the multidisciplinary approach required for our diagnostic framework may not yet be feasible in all memory clinics, and certainly not in most epidemiological studies. However, these proposed criteria acknowledge the progress that has been made in the last two decades in refining our understanding of the neurobiology and clinical phenomenology of AD. Their usefulness will be determined in the future as investigators apply the criteria in a variety of research studies and as key issues in their application are resolved. ■

Table 1: Diagnostic Criteria for Alzheimer's Disease

Probable AD: A plus one or more supportive features B, C or D
Core Diagnostic Criteria
A. Presence of an early and significant episodic memory impairment that includes the following features: 1. Gradual and progressive change in memory function reported by the patient or informant over more than six months. 2. Objective evidence of significantly impaired episodic memory on testing. This generally consists of memory performance that does not improve significantly with cueing or recognition testing and after effective encoding of information has been previously controlled. 3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances.
Supportive Features
B. Presence of MTL atrophy: Volume loss of hippocampi, entorhinal cortex or amygdala evidenced on MRI with: • qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms).
C. Abnormal CSF biomarkers: • decreased Aβ 1–42 and/or increased total tau and/or increased phospho-tau; • other well validated markers to be discovered in the future.
D. Specific pattern in functional neuroimaging with PET: • reduced glucose metabolism in bilateral temporal parietal regions; • other well validated ligands, including those that will emerge such as PiB or FDDNP.
Exclusion Criteria
History: • sudden onset; • early occurrence of the following symptoms – gait disturbances, seizures, behavioural changes.
Clinical features: • focal neurological features including hemiparesis, sensory loss, visual field deficits; • early extrapyramidal signs.
Other medical conditions severe enough to account for memory and related symptoms: • non-AD dementia; • major depression; • cerebrovascular disease; • toxic and metabolic abnormalities, all of which may require specific investigation; • MRI FLAIR or T2 signal abnormalities in the MTL that are consistent with infectious or vascular insults.

AD = Alzheimer's disease; MTL = medial temporal lobe; CSF = cerebrospinal fluid; PET = positron emission tomography; PiB = Pittsburgh Compound B; FDDNP = 2-(1-{6-[(2-[F18]fluoroethyl) (methyl) amino]-2-naphthyl}ethylidene) malononitrile; MRI FLAIR = magnetic resonance imaging fluid attenuation inversion recovery.