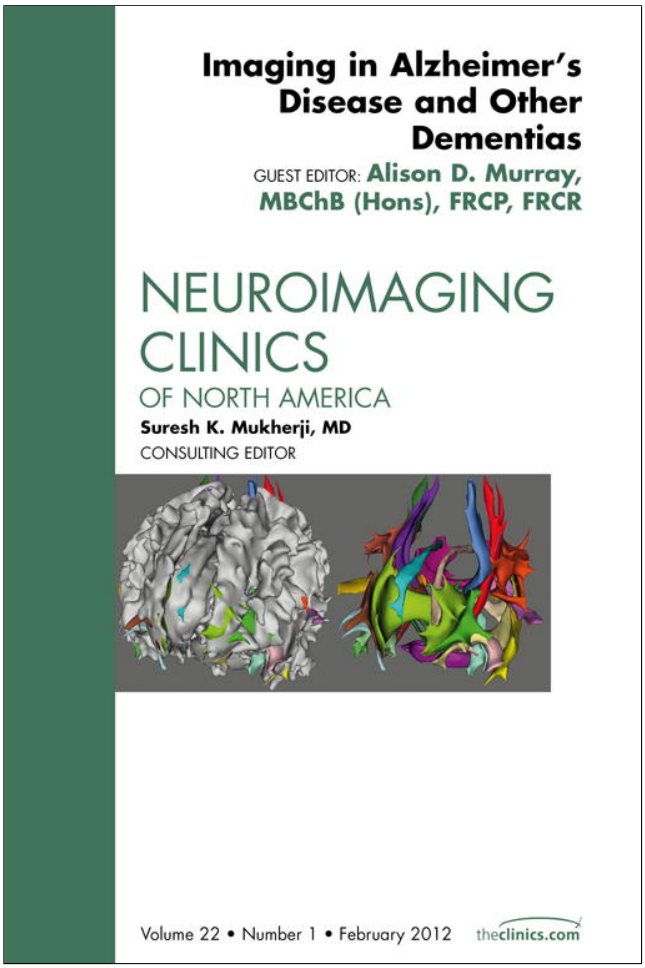

Clinical and Research Diagnostic Criteria for Alzheimer's Disease

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NEW CONCEPTS FOR THE CLINICAL DEFINITION OF ALZHEIMER'S DISEASE

For more than 25 years, the diagnosis of Alzheimer's disease (AD) has been based on the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria, according to which the diagnosis is classified as definite (clinical diagnosis with histologic confirmation), probable (typical clinical syndrome without histologic confirmation), or possible (atypical clinical features but no alternative diagnosis apparent; no histologic confirmation).[1] According to this definition, clinicians used the term AD to refer to a clinical dementia entity that typically presents with a characteristic progressive amnestic disorder with the subsequent appearance of other cognitive and neuropsychiatric changes that impair social function and activities of daily living.[2] In the NINCDS-ADRDA criteria, biological investigation (blood and cerebrospinal fluid [CSF]) and neuroimaging examination (computed tomography [CT] scan or magnetic resonance [MR] imaging) were only proposed to exclude other causes of the dementia syndrome (eg, vascular lesions, tumors, infectious or inflammatory processes). Typical sensitivity and specificity values for the diagnosis of probable AD with the use of NINCDS-ADRDA criteria are 81% and 73%, respectively.[3]

The recent advances in biomarkers of AD, which provide in vivo information about the pathophysiologic process associated with AD, have stimulated the proposal of new diagnostic criteria by the International Working Group (IWG) for New Research Criteria for the Diagnosis of AD.[4,5] According to this framework, the diagnosis of AD was reconceptualized as a clinical-biological entity with a specific clinical phenotype and confirmatory in vivo pathophysiologic evidence of AD. This combined clinical and biological approach may improve the accuracy of the diagnosis.[6–8] Because this new diagnostic framework no longer refers to dementia, it permits a clinical diagnosis to be established at an early prodromal/predementia stage of the disease that

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was previously incorporated in the heterogeneous concept of mild cognitive impairment (MCI).

More recently, the National Institute of Aging-Alzheimer's Association (NIA-AA) workgroups published new diagnostic guidelines for AD[9–12] that also incorporate biological and imaging markers to establish an earlier diagnosis of AD.

In both diagnostic criteria,[4,13] a consideration of preclinical stages of AD is proposed, according to which the pathophysiologic process of the disease precedes the clinical manifestations. Because this condition has been studied, but there are no clinical implications at this time, this aspect of AD is not discussed in this article.

IDENTIFICATION OF THE CLINICAL SYMPTOMS OF AD AT AN EARLY STAGE

Progression of Cognitive Symptoms Follows the Progression of the Underlying Cerebral Lesions

The most prominent feature of AD is a decline in cognitive function.[2] In the early stages of AD, critical areas for episodic memory are already affected by neuropathologic changes (neurofibrillary degeneration) in medial temporal regions (hippocampal formations, parahippocampal gyrus, and entorhinal cortex). As a consequence, episodic memory deficit is an initial and reliable neuropsychological marker of AD.[14,15] Memory impairment of recent events, unusual repeated omissions, and difficulty in learning new information characterize the first clinical signs. As the disease progresses, the clinical symptoms may involve language disorders, visuospatial and recognition deficits, and difficulties in executing more complex tasks of daily living, leading to dementia.[2] The progression of cognitive deficits is consistent with the extension of underlying pathologic lesions (more specifically, of tau lesions) through the neocortical associative areas, as established by Braak and Braak.[14]

Amnesic Syndrome of the Medial Temporal Type as a Marker of Hippocampal Damage

A limit for establishing an early AD diagnosis concerns the ability to identify the specific pattern of memory disorders in relation to damage to the hippocampal formations that characterize the disease and to distinguish them from age-related attention disorders, or from retrieval deficits that are seen in depression, frontal lobe dysfunction, subcortical dementia, or some vascular dementias. The neuropsychological testing, when adequate memory tests are used, can quantify and qualify the memory deficit and can therefore distinguish genuine memory impairment (eg, failure of information storage and new memory formation) from attention or retrieval disorders (such as normal aging or frontal disorders) (Fig. 1). More

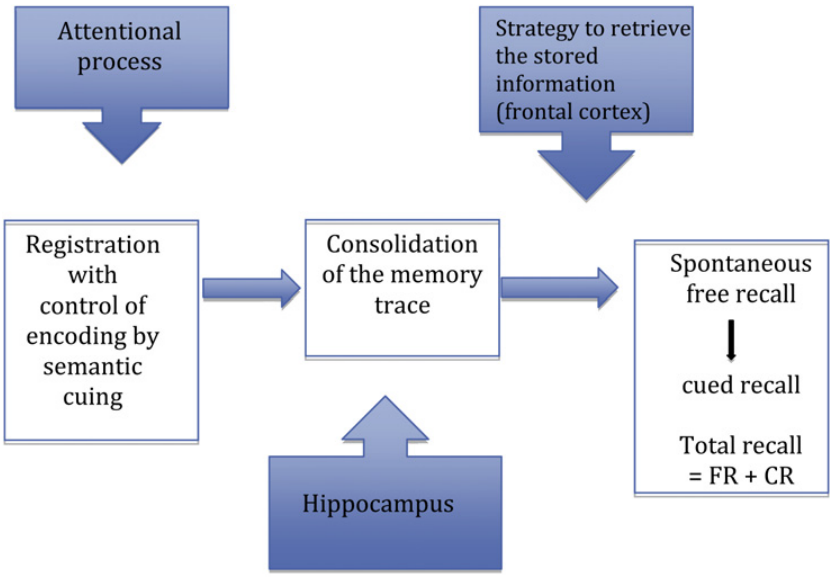

Fig. 1. Principle of examination of verbal episodic memory. The neuropsychological paradigm of the Free and Cued Selective Reminding Test (FCSRT) is based on the 3 different components of episodic memory: registration (by ensuring that all the items have been registered), storage, and retrieval. Verbal episodic memory is assessed by the spontaneous recall of items after delay, and the cued recall, by providing the semantic cues for facilitating access to stored information. Total recall, which is the sum of the spontaneous and the cued recalls, reflects the amount of information that is stored by the patient. A low total recall (ie, low free recall with an inefficiency of cueing [<71%]) suggests a deficit in storage caused by hippocampus damage, whereas a low free recall normalized by cueing (normal total recall) suggests a deficit in retrieval strategy caused by subcortical-frontal dysfunction. CR, cued recall; FR, free recall.

particularly, test paradigms that provide encoding specificity are of great interest and improve the diagnostic accuracy.[5] Within such memory paradigms, test materials are encoded along with specific cues (eg, semantic cues) that are used to control for an effective encoding and are subsequently presented to maximize retrieval. Memory tests that coordinate encoding and retrieval processes include the Free and Cued Selective Reminding Test (FCSRT) or similar cued recall paradigms.[16,17] The FCSRT can identify the amnesic syndrome of the medial temporal type (also called the hippocampal type) observed in AD, defined by (1) poor free recall (as in any memory disorders) and (2) decreased total recall caused by an insufficient effect of cueing. The low performance of total recall despite retrieval facilitation indicates poor storage of information. Measures of sensitivity to semantic cueing can successfully differentiate patients with AD from healthy controls, even when patients are matched to controls on their Mini-Mental State Examination (MMSE) scores or when disease severity is mild.[16,18,19] By isolating patients with an amnesic syndrome of the hippocampal type among those with MCI, the FCSRT is able to distinguish patients at an early stage of AD from MCI nonconverters with high sensitivity (80%) and specificity (90%).[19]

In an AD population, a recent MR imaging study showed that the performance of the FCSRT was correlated with the left medial temporal lobe volume assessed both by voxel-based morphometry analysis and the automatic volumetric method, reinforcing the idea that the measure of episodic memory by this test may be considered a useful clinical marker of medial temporal damage.[20] These correlations within the hippocampus were specially localized in the CA1 field, a region known to be involved in memory storage,[21] and to be affected early by AD neurobiological processes.[22]

The amnestic syndrome of the medial temporal type differs from functional and subcorticofrontal memory disorders, which are characterized by a low free recall performance with a normalization (or a quasinormalization) of the performance in total recall because of good efficacy of cueing.[23] This subcortical-frontal profile of memory impairment is observed in depression,[24] vascular dementia,[25] frontotemporal dementia,[26] and subcortical dementia,[23] showing its additional value for differential diagnosis.

Neuropsychological tests should also assess other cognitive functions that may be affected even at a mild stage of the disease, such as executive functions, visuospatial capacities, language, or semantic knowledge.

Severity of Disease

Different stages of severity are described in AD, from mild to moderate and severe dementia. In the recent AD criteria,[4,5,9] the terms prodromal AD, predementia AD, or AD at the stage of MCI (MCI caused by AD) were proposed in reference to the early stage of the disease.

The MMSE assesses global cognitive efficiency and it is generally used to evaluate dementia severity. Although MMSE is not a specific neuropsychological test for AD diagnosis, it is easy and quick to administer and can track the overall progression of cognitive decline. Longitudinal studies have shown that the mean annual rate of progression of cognitive impairment using MMSE is approximately 2 to 6 points. The Clinical Dementia Rating Scale (CDR), based on an overall evaluation of the patient's condition, offers incremental stages of severity.[27] Functional decline increases with disease progression. In the MCI stage, the patient can live alone. In mild stages of AD, patients require limited home care. In moderate stages, patients need supervision and regular assistance in most activities. In severe stages, residential health care may be required.

BIOMARKERS OF AD

The term biomarkers refers to "an objective measure of a biological or pathogenic process that can be used to evaluate disease risk or prognosis, to guide clinical diagnosis or to monitor therapeutic interventions."[28] These biomarkers include both neuroimaging and biological tools.

Structural Imaging Based on MR Imaging: Atrophy of Medial Temporal Structures as a Topographic and Neurodegenerative Marker

For many years, the use of CT and MR imaging in the evaluation of AD has been proposed for excluding neurosurgical lesions, such as brain tumors or subdural hematomas, or cerebrovascular lesions (cerebral infarcts, white matter lesions, microbleeds) that may account for vascular dementia. Modern neuroimaging extends beyond this traditional role of excluding other conditions and MR imaging is now considered an essential part of AD diagnosis.

The volume of the hippocampus is significantly reduced in AD compared with age-matched control subjects, by 30% to 40% in moderate AD, 15% to 30% in mild AD (MMSE >20), and about 10% to 12% in early AD (MMSE about 27).[29,30] Atrophy of medial temporal structures detected by high-resolution MR imaging is considered to be a reliable diagnostic marker at the

MCI stage,[29,30] and supports the diagnosis of AD.[5] A recent meta-analysis estimated that medial temporal atrophy has 73% sensitivity and 81% specificity for predicting whether patients with amnestic MCI will convert to dementia.[31] In the more advanced stage of AD, atrophy in temporal, parietal, and frontal neocortices is associated with language, praxic, visuospatial, and behavioral impairments.[32]

Cortical atrophy, especially hippocampal atrophy, assessed by MR imaging is considered a topographic biomarker.[4,29] Neuropathologic studies in patients with AD showed that the hippocampal volume measured in vivo by MR imaging correlates with tau deposition, Braak stage, and neuronal counts.[33] Moreover, atrophy of medial temporal structures was correlated with memory deficit.[20]

However, medial temporal atrophy is not specific enough to serve as an absolute criterion for the clinical diagnosis of AD at the MCI stage.[29] A decreased volume of the hippocampus can be observed in neurodegenerative conditions other than AD, even in depression and normal aging. The overlap of hippocampal volume measures between AD and normal aging limits its interpretation when considered without clinical data.

To facilitate clinical investigation, several rating scales have been developed to quantify the degree of medial temporal lobe atrophy by visual inspection of coronal T1-weighted MR imaging. Visual rating scales provide 80% to 85% sensitivity and specificity to distinguish patients with AD from those with no cognitive impairment.[34,35] These scales are widely used and can predict the risk of conversion to dementia in the MCI population.[34,35] New automated methods of segmentation are also valuable tools for measuring hippocampal volume[36,37] and may be useful in clinical practice in the future.

The combination of other markers (such as CSF biomarkers) with measures of hippocampal volume increases the accuracy of a diagnosis of early AD. However, rates of change in several structural measures, including whole brain, entorhinal cortex, hippocampal, and temporal lobe volumes, as well as ventricular enlargement, correlate closely with changes in cognitive performance, supporting their validity as markers of disease progression.[29]

Single-Photon Emission CT and Fluorodeoxyglucose Positron Emission Tomography as a Marker of Neuronal Dysfunction

Functional neuroimaging techniques include measurement of blood flow (^{99m}Tc-hexamethylpropyleneamine oxime [HMPAO] or ^{133}Xe) with single-photon emission CT (SPECT), and positron emission tomography (PET).

SPECT has the advantage of greater availability than PET imaging but PET provides images with higher resolution. ^{99m}Tc-HMPAO SPECT is a useful neuroimaging technique for distinguishing AD from frontotemporal dementia (FTD) but a systematic review reported a clinical accuracy for patients with AD versus control individuals of only 74%.[38] However, recent work in a group with amnestic MCI showed that an automated quantitative tool for brain perfusion SPECT images using the mean activity in right and left parietal cortex and hippocampus was able to distinguish patients at an early stage of AD from patients with stable MCI (sensitivity, specificity, and accuracy of 82%, 90%, and 89%, respectively).[39]

PET with fluorodeoxyglucose (FDG) to measure glucose metabolism has shown good accuracy in distinguishing patients with AD, even at an early stage, from both normal control individuals and patients with non-AD dementias. This imaging method has been approved in the United States for diagnostic purposes. A meta-analysis has reported a sensitivity and specificity of 86% for the diagnosis of AD, although there were wide variations between studies.[40] A reduction of glucose metabolism in bilateral temporal parietal regions and in the posterior cingulate cortex is the most common finding in AD.[5,9,12]

CSF Amyloid and Tau Levels as Pathophysiologic Markers

The challenges for establishing an early diagnosis and for the development of disease-modifying drugs have created a need for biomarkers that reflect core pathologic elements of the disease.[28] The 2 core pathologic hallmarks of AD are (1) amyloid plaques, mainly composed of a heart of aggregated β-amyloid (Abeta) protein; and (2) neurofibrillary tangles (NFT), composed of abnormally hyperphosphorylated forms of the tau protein. In AD, the biomarkers that have been developed reflect amyloid and neurofibrillary tangle abnormalities. Because CSF is in direct contact with the extracellular space of the brain, the CSF is the optimal source of biological physiopathologic biomarkers.[28] The CSF levels of total tau (T-tau), phosphorylated tau (P-tau), and β-amyloid peptide 1-42 (Ab) can distinguish controls from individuals with AD, with a sensitivity and specificity between 80% and 90% even in the early stages of the disease.[28] In autopsy-proven AD, the P-tau/Ab ratio has the best sensitivity (91.6%) and specificity (85.7%) for differentiating AD from normal aging.[41] The

combination of low Ab and high levels of T-tau and P-tau, or, more specifically, the abnormal ratio of Ab to P-Tau, are associated with high rates of progression from amnestic MCI to AD dementia with a sensitivity of 95% and a specificity of 87%.[42]

Neuropathologic studies that analyzed correlations between the levels of in vivo CSF biomarkers

Box 1
Research criteria for the diagnosis of AD: revising the NINCDS-ADRDA criteria

Probable AD: A plus 1 or more supportive features (B, C, D, or E)

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 patients or informants for more than 6 months
   2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalize with cueing or recognition testing and after effective encoding of information has been 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 medial temporal lobe atrophy: volume loss of hippocampi, entorhinal cortex, amygdala shown on MR imaging with qualitative ratings using visual scoring (referenced to well-characterized population with age norms) or quantitative volumetry of regions of interest (referenced to well-characterized population with age norms)

C. Abnormal CSF biomarker: low amyloid β1-42 concentrations, increased total tau concentrations, or increased phosphorylated tau concentrations, or combinations of the 3 (or other well-validated markers that have yet to be discovered)

D. Specific pattern on functional neuroimaging with PET

   Reduced glucose metabolism in bilateral temporal parietal regions

   Other well-validated ligands, including those that are expected to emerge, such as PiB or fluoroethyl-methylamino-2-naphthylethylidenemalononitrile

E. Proven AD autosomal dominant mutation within the immediate family

Exclusion criteria

History

   Sudden onset

   Early occurrence of the following symptoms: gait disturbances, seizures, behavioral changes

Clinical features

   Focal neurologic features including hemiparesis, sensory loss, visual field deficits

   Early extrapyramidal signs

Other medical disorders 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 investigations

   MR imaging fluid-attenuated inversion recovery or T2 signal abnormalities in the medial temporal lobe that are consistent with infectious or vascular insults

From Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:738; with permission.

with the intensity of the postmortem cerebral lesions found correlations between CSF Ab with amyloid plaque load and between CSF T-tau and P-tau with neurofibrillary tangles.[41,43] In a recent work using the new IWG criteria,[4,5] high CSF T-tau and P-tau, but not CSF Ab, were correlated with hippocampal atrophy, suggesting that CSF tau markers are related to the neuronal loss associated with AD.[44]

The combined analysis of the CSF biomarkers, specially the ratio P-tau/Ab, is also helpful for the differential diagnosis between AD and frontotemporal lobar degeneration (FTLD), whatever its behavioral presentation (FTD) or semantic dementia.[45] CSF biomarkers are able to distinguish FTLD with a sensitivity and specificity of around 90%. These results are similar to those from a previous study of patients with FTD shown at autopsy or by genetic studies.[46]

Pittsburgh Compound B PET Imaging as a Pathophysiologic Marker of Brain Amyloid Deposition

Amyloid imaging with PET represents a major advance in AD diagnosis, by enabling the detection and quantification of pathologic protein aggregations in the brain. Pittsburgh compound B labeled with carbon 11 (^{11}C-PiB), an analogue of the amyloid-binding thioflavin-T, is the most extensively studied and best validated tracer. ^{11}C-PiB binds specifically to fibrillar β-amyloid (Aβ) deposits, amyloid plaques, and vascular amyloid, but not appreciably to other protein aggregates such as NFTs or Lewy bodies.[47] ^{11}C-PiB binds nonspecifically to white matter, likely because of delayed clearance of the lipophilic compound from white matter.[48] Using clinical diagnosis as the gold standard, the sensitivity of ^{11}C-PiB for AD diagnosis has been reported as 80% to 100%, with most studies reporting sensitivities of 90% or greater.[49,50]

In most patients, the distribution of tracer uptake is diffuse and symmetric. The highest tracer uptake is consistently found in the prefrontal cortex, precuneus, and posterior cingulate cortex, closely followed by lateral parietal and temporal cortex and striatum, with lower tracer uptake in occipital cortex, globus pallidus, and thalamus.[50,51] ^{11}C-PiB-PET can identify patients with MCI who have amyloid deposition and who may be considered to be at an early clinical phase of AD. Longitudinal studies showed that patients with MCI with significant ^{11}C-PiB retention are at higher risk of developing AD dementia, in contrast with patients with MCI without significant ^{11}C-PiB retention.[52,53] ^{11}C-PiB-PET may be useful to distinguish cognitive deficit caused by AD from non-AD cognitive deficit.

PET imaging with ^{11}C-PiB may be useful in identifying atypical forms of AD, presenting either as a logopenic primary progressive aphasia[54] or a posterior cortical atrophy.[55,56] ^{11}C-PiB can also detect amyloid deposition in other dementia syndromes associated with β-amyloidosis to varying degrees, including cerebral amyloid angiopathy,[51] or Lewy body dementia (LBD).[57] In addition, amyloid PET imaging can improve the differential diagnosis of AD from FTD.[58] The significance of a negative ^{11}C-PiB scan in a patient clinically diagnosed with AD is not yet clear, but it may be explained by ^{11}C-PiB binding that it is insufficient for in vivo detection.[51]

INCORPORATING NEW TOOLS FOR THE DIAGNOSIS OF AD: THE NEW AD CRITERIA

In contrast with the previous AD diagnostic criteria published in 1984, the new IWG criteria[4,5]

Table 1
Categorization of AD biomarkers

	NIA-AA Recommendations (2011)		IWG Criteria (2007, 2010)	
	Biomarkers of Ab Deposition	Biomarkers of Neuronal Injury	Pathophysiologic Markers	Topographic Markers
CSF Ab42	Yes	No	Yes	No
CSF tau/P-tau	—	Yes	Yes	No
PET amyloid imaging	Yes	—	Yes	No
HV or MTLA by MR imaging	No	Yes	No	Yes
Rate of brain atrophy	No	Yes	No	Yes
FDG-PET	No	Yes	No	Yes
SPECT perfusion imaging	No	Yes	No	Yes

Abbreviations: HV, hippocampal volume; MTLA, medial temporal lobe atrophy.

incorporated biomarkers of the underlying pathophysiologic process in the diagnostic framework. The combination of clinical and biological approaches allows the establishment of a clinical diagnosis of AD without having to wait until a dementia syndrome develops. In this view, AD does not overlap with the concept of dementia. AD is considered to be a progressive neurodegenerative disease, and the diagnosis of the disease is possible at an early stage when the patient remains independent and the cognitive symptoms are still mild. The core clinical criteria for AD dementia will continue to be the cornerstone of the diagnosis in clinical practice, but new diagnostic proposals[4,10] advise inclusion of evidence from pathophysiologic

Table 2
Recommendations from the National Institute of Aging on diagnostic guidelines for AD by using biomarkers

Diagnosis of AD at the MCI Stage			
MCI Criteria Incorporating Biomarkers			
Diagnostic Category	**Biomarker Probability of AD Cause**	**Aβ (PET or CSF)**	**Neuronal Injury (tau, FDG, sMR Imaging)**
MCI: core clinical criteria	Uninformative	Conflicting/ indeterminate/ untested	Conflicting/ indeterminate/ untested
MCI caused by AD: intermediate likelihood	Intermediate	Positive Untested	Untested Positive
MCI caused by AD: high likelihood	Highest	Positive	Positive
MCI unlikely to be caused by AD	Lowest	Negative	Negative
Diagnosis of AD at the Dementia Stage			
AD Dementia Criteria Incorporating Biomarkers			
Diagnostic Category	**Biomarker Probability of AD Cause**	**Aβ (PET or CSF)**	**Neuronal Injury (CSF tau, FDG-PET, sMR Imaging)**
Probable AD dementia			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With 3 levels of evidence of AD pathophysiologic process	Intermediate Intermediate High	Unavailable or indeterminate Positive Positive	Positive Unavailable or indeterminate Positive
Possible AD dementia (atypical clinical presentation)			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With evidence of AD pathophysiologic process	High but does not rule out second cause	Positive	Positive
Dementia unlikely to be caused by AD	Lowest	Negative	Negative

Abbreviations: Aβ, amyloid β peptide; sMR imaging, structural MR imaging.

From Albert MS, Dekosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:278; with permission [Diagnosis of AD at the MCI Stage]; and McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:267; with permission [Diagnosis of AD at the Dementia Stage].

biomarker(s) to enhance the specificity of the diagnosis of AD dementia.

Concerning the interpretation of biomarkers in clinical practice, the recent recommendations from the NIA-AA[11] differ in some points from those of the IWG (**Box 1**, **Tables 1** and **2**).[4] The NIA-AA criteria propose the division of biomarkers into 2 major categories: (1) the biomarkers of Ab accumulation, that is, abnormal tracer retention on amyloid PET imaging and low CSF Ab; and (2) the biomarkers of neuronal degeneration or injury, that is, increased CSF tau (both total and phosphorylated tau), decreased FDG uptake on PET in a specific topographic pattern involving temporoparietal cortex, and atrophy on structural MR imaging, again in a specific topographic pattern, involving mainly medial temporal lobes and parietal cortices.[11] The NIA-AA criteria are described in 2 phases, according to the severity of the disease. In the symptomatic predementia (MCI) phase, biomarkers are used to establish the underlying cause of the clinical deficit. Different terminology is proposed for classifying individuals with MCI caused by AD with varying levels of certainty (see **Table 1**). In the dementia phase, biomarkers are used to assess the level of certainty of the underlying AD pathophysiologic process in a given patient.

In the proposals of the IWG criteria,[4,5] the diagnosis relies on (1) a major clinical criterion, which is based on the identification of a predominant episodic memory impairment, with evidence of a progressive amnestic syndrome of the hippocampal type; and (2) evidence of in vivo markers of AD, which can include CSF biomarkers (Ab, T-tau, P-tau), retention of specific PET amyloid tracers, medial temporal lobe atrophy on MR imaging, and/or temporal/parietal hypometabolism on FDG-PET. The diagnosis of AD can also be established in cases of proven AD autosomal dominant mutation. This working group[4] categorizes AD biomarkers as (1) pathophysiologic markers, including CSF biomarkers and PiB-PET, which correspond with the 2 causal degenerative processes that characterize Alzheimer's pathology (the amyloidosis path to neuritic plaques and the tauopathy path to neurofibrillary tangles); and (2) topographic markers that correspond with the downstream markers of neurodegeneration of the NIA-AA criteria, including MR imaging atrophy and FDG-PET, which assess the less specific downstream brain changes that correlate with the regional distribution of Alzheimer's pathology. Concerning the early (predementia) stage of AD, the new lexicon suggests using the term prodromal AD. To avoid confusion, the term MCI should be restricted to individuals who deviate from the clinicobiological phenotype of prodromal AD because they have memory symptoms that are not characteristic of AD or they are biomarker negative (or not available).[4]

Moreover, focal atypical presentation of AD, such as posterior cortical atrophy and logopenic aphasia, have been described in neuropathologic studies.[59] By using physiopathologic markers, such as CSF biomarkers and ^{11}C-PiB-PET, it is now possible to identify in vivo an underlying process similar to that observed in typical AD.[45,55,56] It is proposed that these clinical presentations, without predominant amnesia, should be called atypical AD.[4]

The clinical validity of these new diagnostic criteria is currently being discussed. Extensive work on biomarker standardization is needed before widespread adoption of these recommendations at any stage of the disease. No cutoff or normal/pathologic threshold is clearly defined for each biomarker. Much additional work needs to be done to validate the application of biomarkers as they are proposed in the published articles. Moreover, there is a need for a decisional algorithm for the clinical diagnosis that would guide clinicians in the choice of an invasive investigation such as CSF biomarkers or an expensive examination such as PET imaging.

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