Updates to Diagnostic Guidelines for Alzheimer's Disease

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An expert panel charged by the US National Institutes of Health National Institute on Aging and the Alzheimer's Association has proposed revised clinical diagnostic criteria for dementia due to Alzheimer's disease for the first time since 1984,[1–3] as well as new research criteria for the predementia stages of Alzheimer's disease. The changes reflect new scientific understanding that Alzheimer's disease has a lengthy predementia prodrome as well as new research information about the potential significance of biomarkers.

The original 1984 clinical criteria for Alzheimer's disease required the presence of a dementia syndrome and were based exclusively on clinical symptoms: according to a literal interpretation of these criteria, people free of dementia did not have Alzheimer's disease.[4] To encompass the full continuum of the disease as we now understand it, the expert panel recently developed diagnostic guidelines for mild cognitive impairment (MCI) and "preclinical" stages of Alzheimer's disease, as well as for dementia due to Alzheimer's disease. The dementia and MCI guidelines are offered for clinical use, whereas the preclinical guidelines were developed for research purposes and were intentionally made both provisional and flexible to allow for future advances coming from emerging technologies and understanding of biomarkers.

Biomarkers are defined as physiological, biochemical, or anatomic parameters measured in vivo that reflect specific features of disease-related pathophysiology. Current evidence suggests that some Alzheimer's disease biomarkers may begin to be abnormal 10 to 20 years before clinical symptoms are evident. The guidelines split biomarkers of Alzheimer's disease into 2 categories: (1) markers of brain amyloid and (2) markers of neuronal injury. Currently, the most readily available biomarkers for amyloid predominantly include amyloid positron emission tomography (PET) imaging and cerebrospinal fluid measures of amyloid β (Aβ). The biomarkers of neuronal degeneration or injury include measures of cerebrospinal fluid tau (both total and phosphorylated tau), brain tissue metabolic activity as measured by fluorodeoxyglucose (FDG) uptake changes in PET scan, and atrophy as measured on structural magnetic resonance imaging (MRI) in patterns consistent with Alzheimer's disease. A more comprehensive list of the major biomarkers under investigation in Alzheimer's disease is provided in Table 1.[2] Although biomarkers are increasingly employed in the research setting, their routine clinical use requires further testing and validation.

THE PRECLINICAL STAGE OF ALZHEIMER'S DISEASE

The preclinical stage of Alzheimer's disease describes the phase when clinical symptoms are not yet evident, but biological markers of the disease are present. Given the absence of clinical symptoms, biomarkers are necessary to establish the presence of the disease process, including amyloid buildup and other early nerve cell changes. In some individuals in the preclinical phase of Alzheimer's disease, change in glucose utilization or presence of amyloid deposition and cerebrospinal fluid levels of amyloid or tau proteins can already be detected. Intervention at this stage may be more likely to achieve disease modification.

Because the biomarker data are not fully developed or standardized, the risk for progression to Alzheimer's dementia is unknown for these individuals in the preclinical stage. Thus, use of these imaging and biomarker tests at this stage are recommended only for research at this time.

MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE

The guidelines for MCI due to Alzheimer's disease, although largely intended for research purposes, expand on existing clinical guidelines. The new criteria classify MCI into 3 categories: (1) MCI core clinical criteria, (2) MCI due to Alzheimer's disease (intermediate or high probability), and (3) MCI unlikely due to Alzheimer's disease (Table 2).[2] While the presence of core clinical symptoms defines the presence of MCI, testing of biomarkers is used to further gauge the probability that the MCI is an early manifestation of Alzheimer's disease. The MCI core clinical criteria are defined by symptoms of cognitive impairment (typically memory problems) that are evident and measurable but do not compromise independence. Objective evidence of impairment is present, as measured by cognitive

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CLINICAL POINTS

- The new guidelines for dementia and mild cognitive impairment are offered for clinical use, whereas the preclinical guidelines were developed for research purposes.
- New guidelines were intentionally made both provisional and flexible to allow for future advances coming from emerging technologies and understanding of biomarkers.

Table 1. Biomarkers Under Examination for Alzheimer's Disease[a]

Biomarkers of amyloid β deposition
Cerebrospinal fluid amyloid β_{42} peptide
Positron emission tomography amyloid imaging
Biomarkers of neuronal injury
Cerebrospinal fluid tau/phosphorylated-tau
Hippocampal volume or medial temporal atrophy by volumetric measures or visual rating
Rate of brain atrophy
Fluorodeoxyglucose–positron emission tomography imaging
Single photon emission tomography perfusion imaging
Less well-validated biomarkers: functional magnetic resonance imaging activation studies, resting blood oxygen level–dependent functional connectivity, magnetic resonance imaging perfusion, magnetic resonance spectroscopy, diffusion tensor imaging, and voxel-based and multivariate measures
Associated biochemical change
Inflammatory biomarkers (cytokines)
Oxidative stress (isoprostanes)
Other markers of synaptic damage and neurodegeneration such as cell death

[a]Reprinted with permission from Albert et al.[2]

Table 2. Mild Cognitive Impairment (MCI) Criteria Incorporating Biomarkers[a]

Diagnostic Category	Biomarker Probability of AD Etiology	Aβ (PET or cerebrospinal fluid)	Neuronal Injury (tau, FDG, sMRI)
MCI core clinical criteria	Uninformative	Conflicting/indeterminant/untested	Conflicting/indeterminant/untested
MCI due to AD—intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD—high likelihood	Highest	Positive	Positive
MCI unlikely due to AD	Lowest	Negative	Negative

[a]Reprinted with permission from Albert et al.[2]
Abbreviations: AD = Alzheimer's disease, Aβ = amyloid β peptide, FDG = fluorodeoxyglucose, PET = positron emission tomography, sMRI = structural magnetic resonance imaging.

Table 3. Summary of Clinical and Cognitive Evaluation for Mild Cognitive Impairment Due to Alzheimer's Disease (AD)[a]

Establish clinical and cognitive criteria
Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (ie, historical or observed evidence of decline over time)
Objective evidence of impairment in 1 or more cognitive domains, typically including memory (ie, formal or bedside testing to establish level of cognitive function in multiple domains)
Preservation of independence in functional abilities
Not demented
Examine etiology of mild cognitive impairment consistent with AD pathophysiological process
Rule out vascular, traumatic, and medical causes of cognitive decline, when possible
Provide evidence of longitudinal decline in cognition, when feasible
Report history consistent with AD genetic factors, when relevant

[a]Reprinted with permission from Albert et al.[2]

testing, in 1 or more cognitive domains. Scores 1 to 1.5 standard deviations below the mean of scores of age-and education-matched peers are typical, but these thresholds are not to be used as cutoffs to make the diagnosis. These guidelines do not specify use of any particular test and allow for clinician flexibility. Cognitive concern expressed by the patient, informant, or clinician is also incorporated in the diagnostic guidelines. To increase the likelihood that the underlying disease is a neurodegenerative disorder consistent with Alzheimer's disease, it is necessary to rule out other systemic or brain diseases that could account for the decline in cognition such as vascular, traumatic, medical, or depressive conditions. This evaluation can be derived from further historical information and other tests including neuroimaging, laboratory studies, or formal neuropsychological testing. A summary of these criteria is outlined in Table 3.[2]

Table 4. Criteria for All-Cause Dementia[a]

Cognitive or behavioral symptoms that
Interfere with the ability to function at work or at usual activities
Represent a decline from previous levels of functioning and performing
Are not explained by delirium or major psychiatric disorder
Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a bedside mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis
The cognitive or behavioral impairment involves a minimum of 2 of the following domains:
Impaired ability to acquire and remember new information. Symptoms include repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, and getting lost on a familiar route
Impaired reasoning and handling of complex tasks, poor judgment. Symptoms include poor understanding of safety risks, inability to manage finances, poor decision-making ability, and inability to plan complex or sequential activities
Impaired visuospatial abilities. Symptoms include inability to recognize faces or common objects or to find objects in direct view despite good acuity and inability to operate simple implements or orient clothing to the body
Impaired language functions (speaking, reading, writing). Symptoms include difficulty thinking of common words while speaking, hesitations, and speech, spelling, and writing errors
Changes in personality, behavior, or comportment. Symptoms include uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, and socially unacceptable behaviors

[a]Reprinted with permission from McKhann et al.[4]

Table 5. Criteria for Probable Alzheimer's Disease (AD)[a]

Meets criteria for dementia, and in addition, has the following characteristics:
Insidious onset; symptoms have a gradual onset over months to years, not sudden over hours or days
Clear-cut history of worsening of cognition by report or observation
The initial and most prominent cognitive deficits are evident on history and examination in 1 of the following categories:
Amnestic presentation: it is 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 at least 1 other cognitive domain
Nonamnestic presentations:
Language presentation: the most prominent deficits are in word finding, but deficits in other cognitive domains should be present
Visuospatial 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 impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present

[a]Reprinted with permission from McKhann et al.[4]

Not all people with MCI will progress to Alzheimer's dementia, and, thus, to establish an intermediate or high probability of MCI due to Alzheimer's disease, biomarkers are used to evaluate the underlying etiology of clinical symptoms. Recommended biomarker tests include measures of elevated levels of tau or decreased levels of Aβ in the cerebrospinal fluid, reduced glucose uptake in the brain as determined by FDG-PET, and atrophy of certain areas of the brain as measured with structural MRI. Although intended primarily for the research setting, these tests may be applied in specialized clinical settings as a diagnostic adjunct to help determine possible causes of MCI symptoms.

ALZHEIMER'S DISEASE DEMENTIA

The 1984 clinical criteria for Alzheimer's disease remain the foundation of the diagnosis in that progressive cognitive decline must be associated with impairment in functioning in daily activities. The new guidelines expand the concept of Alzheimer's dementia beyond memory loss as its primary characteristic and incorporate the possibility that a decline in other aspects of cognition, such as anomia, visuospatial impairment, and impaired executive functioning may be the first symptoms to be noticed. Biomarkers may be used to enhance the specificity of the diagnosis. The new guidelines define all-cause dementia (Table 4) and then classify Alzheimer's disease dementia into 3 categories: (1) probable Alzheimer's disease dementia (Table 5), (2) possible Alzheimer's disease dementia (Table 6), and (3) probable or possible Alzheimer's disease dementia with evidence of supportive biomarkers. The first 2 categories are intended for clinical use, and the third is intended for research purposes at this time. Like MCI, biomarkers are used to increase or decrease the level of certainty that Alzheimer's disease is the cause of the dementia. As the understanding and validity of these tests improve, their application in clinical practice will increase.

PRACTICAL IMPLICATIONS

The new guidelines have limited practical implications at this time until more is known about the predictive and diagnostic values of various biomarkers. However, broadening the scope of dementia due to Alzheimer's disease to include nonmemory cognitive decline will help clinicians appreciate the heterogeneity of the

Table 6. Criteria for Possible Alzheimer's Disease (AD)[a]

Atypical course
Atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline OR
Etiologically mixed presentation
Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence of (1) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment, or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden or (2) features of dementia with Lewy bodies other than the dementia itself or (3) evidence for another neurologic disease or a nonneurologic medical comorbidity or medication use that could have a substantial effect on cognition

[a]Reprinted with permission from McKhann et al.[4]

clinical presentation. Making it clear that there is a lengthy preclinical prodrome will help all of us better understand the natural history of the disease. While biomarker use is proposed only for research purposes, clinicians can consider some biomarker test results to help with the level of certainty of the clinical diagnosis. In our practice, clinically ambiguous patients may undergo FDG-PET, cerebrospinal fluid analysis, and sometimes genotyping to clarify diagnosis. Although our practice does not rely on volumetric imaging to aid in diagnosis, some specialists have incorporated this test. Amyloid PET imaging techniques are now under US Food and Drug Administration review and may become available clinically, which will further enhance the ability to render more specific dementia diagnoses.

The early, predementia stages of Alzheimer's disease probably will provide a significant opportunity for therapeutic intervention, as intervention at this stage may be more likely to achieve disease modification. Thus, the new guidelines represent an essential step forward toward eradicating this disease.

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