AD Diagnostic Guidelines Updated

For the first time in 27 years, clinical diagnostic criteria for Alzheimer disease (AD) dementia have been revised, and research guidelines for earlier stages of the disease have been characterized to reflect a deeper understanding of the disorder. The National Institute on Aging (NIA)/Alzheimer's Association *Diagnostic Guidelines for Alzheimer's Disease*, described in an NIA press release on April 19, outline new approaches for clinicians and provide scientists with more advanced guidance for moving forward with research on diagnosis and treatments.

The previous criteria, released in 1984, were the first to address the disease and described only later stages of dementia. The updated guidelines cover the full spectrum of the disease as it changes over many years. They describe the earliest preclinical stages of the disease, mild cognitive impairment (MCI), and dementia resulting from AD pathology. The guidelines also now address the use of imaging (including PET) and biomarkers in blood and spinal fluid to determine whether changes in the brain and body fluids are attributable to AD. "Alzheimer's research has greatly evolved over the past quarter of a century. Bringing the diagnostic guidelines up to speed with those advances is both a necessary and rewarding effort that will benefit patients and accelerate the pace of research," said NIA Director Richard J. Hodes, MD.

The new guidelines appeared online on April 19 in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association.* They were developed by expert panels convened last year by the NIA and the Alzheimer's Association. Preliminary recommendations were announced at the association's International Conference on Alzheimer's Disease in July 2010, followed by a comment period. Guy M. McKhann, MD (Johns Hopkins University School of Medicine; Baltimore, MD), and David S. Knopman, MD (Mayo Clinic; Rochester, MN), cochaired the panel that revised the 1984 clinical AD criteria. Marilyn Albert, PhD (Johns Hopkins University School of Medicine), headed the panel refining the MCI criteria. Reisa A. Sperling, MD (Brigham and Women's Hospital, Harvard Medical School; Boston, MA), led the panel tasked with defining the preclinical stage. The journal also included a paper by Clifford Jack, MD (Mayo Clinic), et al. on the need for and concepts behind the new guidelines.

The original 1984 clinical criteria for AD defined the disease as having a single stage (dementia), with diagnosis based solely on clinical symptoms. These criteria assumed that people free of dementia symptoms were disease free. Diagnosis could be confirmed only at autopsy, when amyloid plaques and τ protein tangles were found in the brain. Interim research has demonstrated changes in the brain a decade or more before symptoms appear. Of particular interest in the formation of the new guidelines is the now well-validated observation that amyloid deposits begin early in the disease process but that tangle formation and loss of neurons occur later and may accelerate just before clinical symptoms appear. The new guidelines cover 3 distinct stages of AD:

(1) *Preclinical:* The preclinical stage, for which the guidelines apply only in the research setting, describes a phase in which brain changes, including amyloid buildup and other early nerve cell changes, may already be in process. At this point, significant clinical symptoms are not yet evident. In some individuals, amyloid buildup can be detected with PET imaging and/or cerebrospinal fluid (CSF) analysis, but the risk for progression to AD dementia remains undefined. The guidelines recommend use of these imaging and biomarker tests at this stage only for research, not for routine clinical applications.

(2) *MCI:* The guidelines for the MCI stage are also largely for research, although they clarify existing criteria for use in a clinical setting. The MCI stage is marked by symptoms of memory problems, enough to be noticed and measured but not compromising a person's independence, and individuals with MCI may or may not progress to AD dementia. Researchers will particularly focus on standardizing biomarkers for amyloid and for other possible signs of injury to the brain. Current biomarkers include elevated levels of τ or decreased levels of τ-amyloid in the CSF, reduced glucose uptake in the brain as determined by PET, and atrophy of certain areas of the brain as seen with MR imaging. These tests will be used primarily by researchers but may be applied in specialized clinical settings to supplement standard clinical tests to help determine possible causes of MCI symptoms.

(3) *AD dementia:* The guidelines and diagnostic criteria for this final stage of the disease are most relevant for clinicians and patients. They outline ways in which clinicians should approach evaluating causes and progression of cognitive decline. The guidelines also expand the concept of AD dementia beyond memory loss as its most central characteristic. A decline in other aspects of cognition (e.g., word finding, vision/spatial issues, and impaired reasoning or judgment) may be the first symptoms to be noted. At this stage, biomarker test results may be used in some cases to increase or decrease the level of certainty about a diagnosis of AD dementia and to distinguish AD from other dementias, even as the validity of such tests is still under study for application and value in routine clinical practice.

According to the press release, the panels purposefully left the guidelines sufficiently "flexible to allow for changes that could come from emerging technologies and advances in understanding of biomarkers and the disease process itself."

National Institute on Aging