Diagnosis: Clinical, Pathologic, and Radiologic

The most commonly used clinical criteria for the diagnosis of AD are those of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) and those developed in 1984 by a joint task force of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al. 1984); the DSM-IV and the NINCDS-ADRDA criteria are summarized in Tables 2 and 3, respectively. The NINCDS-ADRDA criteria are more detailed and classify AD into definite, probable, and possible levels of diagnostic certainty. The diagnosis of definite AD requires both the clinical features of probable AD and histopathologic confirmation by biopsy or autopsy. Probable AD requires the presence of dementia by clinical examination, documented by standardized mental status assessment and confirmed by neuropsychological tests. There must be demonstrable deficits in at least two areas of cognition, and progressive worsening of memory and other cognitive functions in the absence of delirium. Onset must be between the ages of 40 and 90 years, with no other identifiable systemic or neurological abnormalities that could account for the progressive deficits in cognition. Other features consistent with but not required for a diagnosis of probable AD include progressive deficits in specific cognitive functions (such as language, praxis, recall, perceptual recognition), impaired activities of daily living, a positive family history (particularly with pathologic confirmation), normal or non-specific results in tests such as spinal fluid examination, electroencephalography, and computerized tomography, psychiatric and behavioral abnormalities, weight loss and, in advanced stages of the disease, increased muscle tone, myoclonus, gait abnormalities, and seizures. There is currently no laboratory test to confirm the diagnosis of AD.

Table 2 Summary of DSM-IV criteria for diagnosis of AD (Yaari and Corey-Bloom 2007)

- Insidious onset with progressive decline of cognitive function resulting in impairment of social or occupational functioning from a previously higher level
- Impairment of recent memory and at least one of the following cognitive domains:
  - Aphasia
  - Apraxia
  - Agnosia
  - Executive functioning (planning, organizing, sequencing, abstracting)
- Cognitive deficits are not due to other neurological, psychiatric, toxic, metabolic, or systemic diseases
- Cognitive deficits do not occur solely in the setting of a delirium

Table 3 Summary of NINCDS-ADRDA criteria for diagnosis of AD (Yaari and Corey-Bloom 2007)

Possible AD

- Atypical onset, presentation, or clinical course of dementia
- Presence of another illness capable of producing dementia

Probable AD

- Deficits in two or more cognition domains
- Progressive decline of memory and other cognitive functions
- Preserved consciousness
- Onset between 40 and 90 years of age
- Absence of systemic or other brain disease that could account for symptoms

Definite AD

- Clinical criteria for probable AD
- Tissue diagnosis by autopsy or biopsy

The prevailing neuropathologic criteria for AD are those promulgated by the National Institute on Aging (NIA) and National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) (Mirra et al. 1993). These criteria include minimal neocortical plaque densities that are age-adjusted but do not specify either the plaque type or the neocortical region involved. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria require an age-adjusted semi-quantitative plaque frequency and a clinical diagnosis of dementia for a diagnosis of AD (Mirra et al. 1991). The Reagan consensus recommendations emphasize the presence of both neuritic plaques and neurofibrillary tangles in the neocortex by utilizing a modification of the CERAD criteria in addition to staging tools for neurofibrillary lesions to assign a likelihood of AD (high, intermediate, low) based on pathological findings alone.

It is now generally recognized that the NINCDS-ADRDA and the DSM-IV-TR criteria have fallen behind recent dramatic advances in our scientific knowledge of AD, with reliable biomarkers now available based in structural magnetic resonance imaging (MRI), molecular neuroimaging with positron emission tomography (PET), and cerebrospinal fluid (CSF) analyses (see below) (DuBois et al. 2007). Although the revised criteria NINCDS-ADRDA remain focused on a clinical determination of memory impairment, they also stipulate that there must also be at least one abnormal biomarker among structural neuroimaging with MRI, molecular neuroimaging with PET, and CSF analysis of β-amyloid or tau proteins (DuBois et al. 2007).

Structural MRI in patients with AD or MCI show atrophy in the entorhinal cortex and hippocampus (Figure 1), predictive of future cognitive decline and conversion to AD among individuals with MCI. The degree of entorhinal and hippocampal atrophy by MRI is strongly correlated with the severity of degenerative pathology in these areas at autopsy. It has been suggested, therefore, that MRI volumetry may be a useful imaging adjunct in the diagnosis of AD and may even exceed the diagnostic accuracy of clinical evaluation (Desikan et al. 2009, Duara et al. 2008).

PET is a well-established, widely used molecular imaging modality (Zanzonico 2004) in oncology and cardiology as well as in neurology and psychiatry (Herholz et al. 2007). PET-based imaging techniques include measurement of regional cerebral glucose metabolism (rCMRglc) using the partially metabolized glucose analog fluorine-18 (^{18}F)-labeled 2-fluoro-2-deoxy-D-glucose (FDG). Among the characteristic features of FDG PET brain images of AD patients are significant hypometabolism in the posterior cingulate cortex as well as hippocampal atrophy and associated hypometabolism; other areas of the brain (ie not associated with cognitive function) remain largely unaffected (Figure 4 A). Among patients with MCI, those

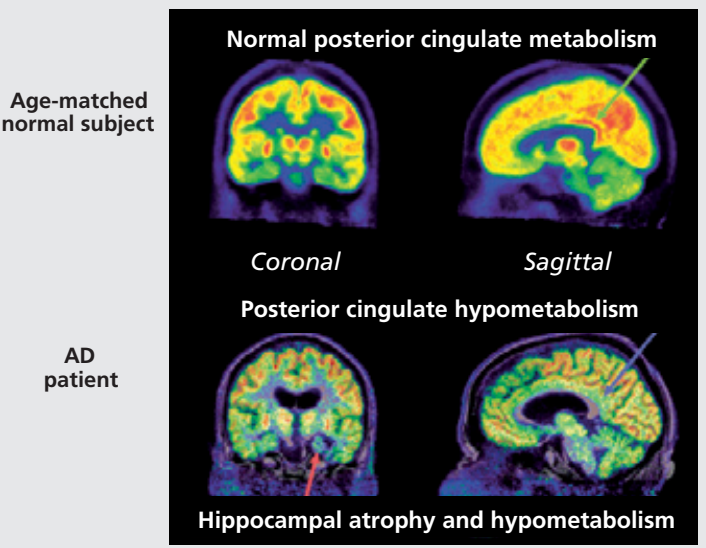

Figure 4 Comparative FDG PET images of the brains of a normal subject (top) and an AD patient (bottom). In the color scale used, yellow and red represent higher and green and blue lower FDG uptakes and rates of glucose metabolism. (Adapted from Herholz et al. 2007, with permission from the British Institute of Radiology.)

likely to convert to AD within the next two years can be identified based on characteristic features in their FDG PET images (Herholz et al. 2007).

The use of radiotracers other than FDG, including carbon-11 (^{11}C)-labeled tracers, is increasing the applicability of PET to the study and diagnosis of dementia and psychiatric diseases generally (Herholz et al. 2007). Importantly, however, FDG is a metabolic tracer and at best a surrogate marker of AD, as it does not visualize its underlying pathology (ie β-amyloid plaques and neurofibrillary tangles). PET imaging tracers which label and thus allow visualization of β-amyloid or tau (τ) protein in vivo are promising approaches to improving the early diagnosis of AD. However, none of these tracers has yet been approved for clinical use and therefore they have not yet been incorporated into the diagnostic criteria for AD. PET ligands for plaque imaging (Figures 5 and 6) are all derived from histological staining agents and currently include ^{11}C-Pittsburgh compound B (PIB) (Klunk et al. 2004), ^{11}C-4-*N*-Methylamino-4′-hydroxystilbene (SB-13), 11C-AZD2184, ^{18}F-2-(1-{6-[(2-fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP) (Thompson et al. 2009), ^{18}F-GE067, ^{18}F-AV-45 (Wong et al. 2008) and ^{18}F-Florbetaben (BAY 94-9172) (Rowe et al. 2008). Based on the favorable clinical results to date, β-amyloid imaging agents will likely enter phase-III evaluation and wider clinical use in the near future[1]. Other compounds, such as ^{11}C-labeled PK-11195, has been used to investigate microglial activation in both AD and MCI subjects (Wiley et al. 2009); but it provides less sensitivity and specificity than amyloid ligands. PET has also been used to investigate neurotransmitter systems in dementia, including the cholinergic, dopaminergic and serotonergic systems. PET will no doubt continue to be important in dementia research and increasingly important in clinical practice as new mo-

1 See: US Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), 2008 Meeting of Advisory Committee on Peripheral and Central Nervous System Drugs, Silver Spring, MD, Oct 23, 2008, web site: fda.gov/ohrms/dockets/ac/cder08.html#PeripheralCentralNervousSystem.