A definitive diagnosis of Alzheimer disease (AD) depends on finding widespread neurofibrillary tangles and plentiful neuritic plaques in the brain of an individual with a clinical diagnosis of progressive dementia.\(^1\) Using contemporary diagnostic criteria, the antemortem diagnosis of probable AD in centers specialized for AD is confirmed 80% to 90% of the time. There is the suspicion, but no firm data, that diagnostic accuracy is much lower outside of practices dedicated to patients with dementia. Furthermore, the diagnostic workup is expensive. In most settings, the evaluation generally includes a careful medical history and physical examination; neurologic examination (and psychiatric consultation as indicated); laboratory blood studies to exclude underlying metabolic and medical illnesses that masquerade as AD; a mental status assessment and formal cognitive tests; and a computed tomographic scan or magnetic resonance imaging of the brain.\(^2\) Because these procedures are time-consuming and costly, there is a need to identify biological tests that can circumvent aspects of this workup and point the physician to the correct diagnosis. It would be highly desirable to measure a substance or substances in blood or urine samples or cerebrospinal fluid (CSF) that would lead to a positive diagnosis of AD without the need for specialized dementia clinics and the expense and time of standard diagnostic evaluations. In response to this need, the Reagan Research Institute of the Alzheimer’s Association and the National Institute on Aging convened a working group in 1997 to examine the status of various antemortem markers for AD. The consensus statement of this group, entitled “Molecular and Biochemical Markers of AD,” was published in 1998.\(^3\) The consensus statement first defined the characteristics of an ideal biomarker, and then outlined the steps required for a proposed biomarker to achieve acceptance by the medical community. Finally, the statement reviewed the current state of all proposed biological markers. The workshop participants observed that none of the current biomarkers had yet achieved universal acceptance and concluded none fully met the consensus criteria for an ideal marker. Nonetheless, several tests were identified as good markers for familial AD, and several other tests showed promise as a diagnostic aid for sporadic AD. The purpose of this review is to put these recommendations into a practical context. What does the consensus statement tell the practicing clinician? How do the opinions in the consensus statement affect clinical practice in diagnosing and treating patients with dementia?

Arch Neurol. 1999;56:281-283

The most successful diagnostic tests for AD are based on advances in molecular genetics, and are limited to early-onset familial AD. Missense mutations in 3 genes—PS1 on chromosome 14, PS2 on chromosome 1, and APP on chromosome 21—all cause familial AD. In all, only a few hundred families carry these identified mutations that cause autosomal dominant AD. Most of these pedigrees have PS1 mutations and onset of dementia at age younger than 50 years;
mutations in the APP gene are rare, and there are only 2 pedigrees with PS2 mutations. From a practical viewpoint, it is reasonable to search for a PS1 mutation in familial AD with very early onset, but searching for missense mutations in individuals with familial AD with onset older than 50 years or in individuals without a family history of AD is rarely worthwhile. In contrast to these deterministic genetic causes of AD, the apolipoprotein E (apoE) ε4 allele is a risk factor for AD. Numerous studies attest to the fact that the ε4 allele is 3 to 4 times more common in AD, including the most common category of late-onset disease without known family history, than in individuals who are not demented. As opposed to the missense mutations, however, the ε4 allele is not a deterministic cause of AD, only a risk factor. Thus, relying on the apoE genotype alone to establish a diagnosis of AD is inadequate because this measure by itself has low sensitivity and specificity. Many individuals, perhaps a majority, who inherit ε4 do not develop AD even at an advanced age. Nonetheless, when used in conjunction with conventional diagnostic workup, finding an ε4 allele adds a small percentage of confidence to the clinical diagnosis.

Genetics aside, the most convincing diagnostic tests will be those that seek to detect in life the histopathologic hallmarks characteristic of AD that are observed in the brain at death. The neurofibrillary tangle and neuritic plaque are the principal lesions associated with AD. The neurofibrillary tangle is composed primarily of hyperphosphorylated tau, which is a cytoskeletal protein. Diffuse amyloid deposits pepper the AD brain; the mature neuritic plaque contains a compacted core of amyloid protein. Much of this amyloid is a 42-amino acid peptide derived from proteolytic cleavage of a larger amyloid precursor protein molecule. This peptide, called Aβ1-42, has putative neurotoxic properties that may initiate a cascade of events leading to neuronal dysfunction and death. As a result of intense investigation into the mechanism whereby tangles and plaques form, antibodies directed toward epitopes of tau and toward different amyloid fragments have been adapted for clinical use. Under normal conditions, a small amount of soluble Aβ1-42 circulates in the bloodstream. In individuals with the deterministic mutations for AD in PS1, PS2, and APP, Aβ1-42 levels in the blood are increased compared with levels in sporadic AD, which generally do not differ from levels measured in individuals without dementia. Although potentially useful in diagnosing familial AD, measuring Aβ1-42 levels in the blood is limited to research laboratories and is not in widespread use. Even if this test were widely available, information to date indicates plasma Aβ1-42 levels would not be diagnostically useful in most patients with nonfamilial or late-onset AD.

The CSF bathes the brain, and is potentially a more accurate representation of what goes on in the brain than measuring tau or Aβ in the peripheral bloodstream. Both tau and amyloid fragments can be measured in CSF; their detection forms the basis for the development of commercial diagnostic tests for AD. There is general consensus that CSF levels of tau are significantly increased in AD compared with both healthy control subjects and patients with non-AD neurologic diseases. Similarly, there is general consensus that levels of Aβ1-42 are characteristically decreased in AD, whereas levels of Aβ total (Aβ1-42 and Aβ1-40) are no different in patients with AD than in control subjects. The crucial question is whether the increases in tau and decreases in Aβ1-42 occur with sufficient frequency and magnitude that they offer diagnostic value. To date, the answer has been no. Both measures suffer from poor accuracy: if sensitivity is set at a satisfactory 80% to 90% level, specificity is low, and vice versa. Combining the 2 measures increase accuracy slightly, but many individual values remain in a diagnostically indeterminate range. A further limitation on using these measures as diagnostic tests is that few cases of dementia with a clinical diagnosis of probable AD and the putative diagnostic profile of low Aβ1-42 and high tau in CSF during life have been confirmed pathologically. Other CSF markers, such as neuronal thread protein, have been proposed as biomarkers for AD, but require independent confirmation. It is likely that refinements on current Aβ1-42, tau, or neuronal thread protein assays will occur as a result of attempts to improve diagnostic accuracy. At present, these tests can be recommended only as an adjunct to comprehensive diagnostic assessment in difficult cases. Confidence in the diagnosis increases when the CSF profile fits that expected in AD, but indeterminate results should be anticipated.

What can we expect from an ideal biomarker for AD? It is probably unrealistic to expect that any biomarker be 100% specific and sensitive for the diagnosis of AD. At autopsy, the brains of many patients with definite AD have other lesions, including infarcts, gliosis, and Lewy bodies. In any given instance, it is difficult to be certain which of these was etiologically important in producing dementia. Clinicians may eventually follow the lead of pathologists, who have adopted a less dichotomous diagnosis of AD vs no AD than in the past. According to the National Institute on Aging and the Reagan Research Institute of the Alzheimer’s Association consensus criteria for the neuropathological diagnosis of AD, the diagnosis of AD is probabilistic. That is to say, the diagnosis of AD is based on a likelihood estimate in which all pathologic findings are described, and the extent and intensity of plaques and tangles graded. If pathologists examining the entire brain are cautious in diagnosing AD unequivocally, then perhaps clinicians, armed with indirect molecular and biochemical measures of plaques and tangles, should be even more reserved. Viewed from this perspective, biological markers of AD may turn out to be more useful in tracking the course of illness and documenting the response to treatment than in diagnosis.

Accepted for publication June 20, 1998.

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REFERENCES


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