Do biomarkers for Alzheimer's disease have utility in everyday practice?

AD remains a clinical diagnosis, but research might change that with specific tests for risk and disease

Guidelines for diagnosing Alzheimer's disease (AD) are undergoing the first major changes since they were developed 30 years ago. The National Institute on Aging (NIA) and the Alzheimer's Association (AA) have established workgroups to revise guidelines that were written in 1984.[1]
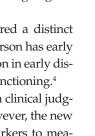
One of the major changes to these new guidelines is mention of research on biomarkers for diagnosing and monitoring progression of dementia in AD. This is an exciting and provocative development, but the questions practitioners who diagnose and treat AD should be asking are whether such biomarkers have utility in clinical practice today, or whether their application is a distant promise of continuing research.
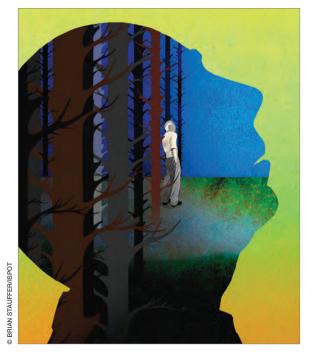
Principles put forward in the guidelines

The new AD guidelines set forth in 3 major papers by the workgroups created by the NIA and AA include a change in nomenclature of AD.[2] The workgroups have sought to define AD with specific stages that include:

• a preclinical/prodromal phase, in which the pathophysiology responsible for future cognitive changes is ongoing but lacks clinical manifestations[3]

• mild cognitive impairment, now considered a distinct entity from dementia and diagnosed when a person has early signs of AD; manifestations of impaired cognition in early disease are not significant enough to affect daily functioning.[4]

These newly formulated stages of AD rely on clinical judgment, and AD remains a clinical diagnosis. However, the new diagnostic guidelines include the use of biomarkers to measure disease progression.

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Table

What are the potential biomarkers of Alzheimer's disease?

Class	Biomarker	Proposed characteristic
Neuroimaging	Fludeoxyglucose (with PET)	Reveals areas of diminished glucose metabolism in the brain
	MRI	Measures hippocampal atrophy and cortical thinning
	Florbetapir F 18 Injection (with PET)	Binds to amyloid β plaques in the brain
CSF markers	Aβ42 protein	Low levels, as the Aβ42 protein is deposited in the brain
	T-tau	Associated with neurodegeneration
	P-tau	Associated with neurodegeneration and neurofibrillary tangles
Serum marker	Aβ42	Proposed as a correlate of CSF measurement to demonstrate increased deposition of Aβ42 in the brain and less deposition in the periphery; correlation is poor
Genetic markers	Amyloid precursor protein Presenilin-1 Presenilin-2	Implicated in autosomal-dominant (early-onset) AD
	Apolipoprotein 4-β4	Allele associated with an increased risk of AD

Aβ42: amyloid β protein; AD: Alzheimer's disease; CSF: cerebrospinal fluid; PET: positron-emission tomography

Source: Reference 7

Biomarkers of normal biologic function and pathology

The Biomarkers Definitions Working Group defines a biomarker as:

> … a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[5]

These characteristics include imaging studies and body fluids, such as serum and cerebrospinal fluid (CSF).

In AD, biomarkers are meant to measure the pathogenic processes of:

- accumulation and deposition of amyloid β protein (Aβ42) plaques
- neuronal degeneration characterized by an increase in phosphorylated tau protein and neurofibrillary tangles.[6]

The purpose of these biomarkers is to identify ongoing disease and help the clinician stage patients who display a spectrum of symptoms.

Four classes of biomarkers (*Table*[7]) have been identified for use in the diagnosis of, and research on, AD:

- neuroimaging
- CSF
- serum
- genetic markers.

Neuroimaging

The basic purpose of CT and MRI of the head in the workup of cognitive impairment is to rule out a lesion in the brain, such as a tumor or hemorrhage, as the cause of, or contributor to, the impairment. Several neuroimaging studies are available to aid in diagnosing AD and distinguishing it from other causes of dementia, including:

- Fludeoxyglucose (FDG) positron-emission tomography (PET) scanning
- MRI
- Florbetapir F 18 Injection for PET.

FDG PET identifies areas of the brain in which glucose metabolism is decreased. This finding is thought to represent synaptic dysfunction.[8] The true clinical utility of FDG PET appears to be as an aid in distinguishing cases of AD from frontotemporal dementia, by identifying regions of metabolic dysfunction.[9] (Note: Medicare will reimburse for FDG PET only if 1) the patient has met diagnostic criteria for *both* AD and frontotemporal dementia for at least 6 months and 2) the cause of symptoms is uncertain.[10])

FDG PET also can be useful in patients with mild cognitive impairment by identifying hypometabolism in the temporal and

parietal regions of the brain years before clinical AD develops.

In addition to FDG, 2 other imaging probes—Pittsburgh compound and 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene) malononitrile (more commonly, FDDNP)—have been used with PET as research tools to demonstrate evidence of AD.[11]

MRI has been used to measure hippocampal atrophy and cortical thinning that occurs as a patient progresses from normal cognitive function or mild cognitive impairment to full dementia.[5] The degree of atrophy has not been well correlated with the degree of functional impairment.

Florbetapir F 18 Injection was approved by the FDA in October 2013, under the brand name AMYViD, for measuring the quantity of Aβ42 deposition in the brain. When injected, this radiopharmaceutical binds to Aβ42 and can be detected on PET.[12] Use criteria for AMYViD PET recently were developed[13]; the technique is indicated as an additional diagnostic tool for ruling out AD.

A negative AMYViD scan indicates sparse or no Aβ42 plaques, and is inconsistent with AD. However, a positive AMYViD scan does *not* establish a diagnosis of AD or other cognitive disorder.[14] This lack of specificity decreases the potential utility of the scan in clinical practice.

Use of AMYViD PET in general practice also is constrained by cost, which varies by location, based on the fee for the PET scan ($1,000 to $3,000)[15]; to that, add the cost of a dose of AMYViD ($1,600, wholesale).[16] The technique is not reimbursable, and the total out-of-pocket expense can be as much as $5,000—making an AMYViD PET prohibitive.

Cerebrospinal fluid markers

CSF biomarkers used in the evaluation of AD are Aβ42, t-tau protein, and p-tau protein.[6,17] It is generally thought that the level of Aβ42 in CSF *decreases* in AD—indicative of Aβ42 being deposited in the brain.[8] Tau proteins are elevated in CSF as neurons are destroyed. P-tau is associated with the neurofibrillary tangles of AD; its presence in CSF is thought to represent an increase in those tangles. The combination of a low level of Aβ42 and an elevated level of p-tau in CSF is considered the signature CSF biomarker of AD.[6]

Serum markers

The search for reliable serum biomarkers of AD is the area of greatest research interest because a blood test is a less invasive form of screening. Regrettably, the utility of serum biomarkers for clinical practice has not been established.

Aβ42 can be measured in serum, but levels do not correlate well with CSF levels.[18] Other serum markers that have been evaluated for clinical utility include measures of lipid metabolism, oxidation, and inflammation. With none of these is there clear correlation between the level of protein and AD.[18]

Fourth front: Genetics

Several alleles are associated with AD. Mutations in amyloid precursor protein, presenilin 1, and presenilin 2 have been shown to cause a change in the processing of Aβ42 and thus lead to AD.[19] These mutations are inherited in an autosomal-dominant fashion and are detected in early-onset (age <65) AD.

Mutations in apolipoprotein 4-β4 also has been the subject of much research; this allele usually is associated with increased risk of the more common, later-onset AD.[20] Some evidence suggests that apolipoprotein 4-β4 carriers who develop AD might be at risk of earlier onset of symptoms, compared to non-carriers,[21] but the clinical significance of that increased risk has not been established.

What utility do biomarkers have?

As we said at the beginning of this article, the question that clinicians should be asking is: "What is the current clinical utility of these sophisticated biomarkers and genetic testing?"

The answer is "little utility." Diagnosing AD is a clinical enterprise, with, as we've outlined, specific and narrow exceptions.

Recently, researchers demonstrated biomarker evidence of AD *before* symptom onset

Clinical Point

The lack of specificity decreases the potential utility of florbetapir F 18 Injection in clinical practice

Biomarkers for Alzheimer's disease

Related Resources

- Blennow K, Dubois B, Fagan AM, et al. Clinical utility of cerebrospinal fluid biomarkers in the diagnosis of early Alzheimer's disease [published online May 5, 2014]. Alzheimers Dement. doi: 10.1016/j.jalz.2014.02.004.
- Chase A. Alzheimer disease: Advances in imaging of AD biomarkers could aid early diagnosis. Nat Rev Neurol. 2014;10(5):239.
- De Riva V, Galloni E, Marcon M, et al. Analysis of combined CSF biomarkers in AD diagnosis. Clin Lab. 2014;60(4):629-634.
- Kristofikova Z, Ricny J, Kolarova M, et al. Interactions between amyloid-β and tau in cerebrospinal fluid of people with mild cognitive impairment and Alzheimer's disease [published online March 26, 2014]. J Alzheimers Dis. doi: 10.3233/JAD-132393.

Drug Brand Name

Florbetapir F 18 Injection • AMYViD

in patients who have known autosomal-dominant gene mutations for AD.[19] There is no evidence, however, that these biomarkers are useful for screening the general population to identify people who 1) are at risk of, or who have, AD and 2) do not have AD.

That being said, CSF and imaging biomarkers of AD are being used in clinical settings in some European countries to aid investigation of cognitive decline.

In conclusion

Here are key points to take away from this discussion of biomarkers of AD:

- The utility of these biomarkers today is in research—although some of them might, on occasion, be useful to distinguish dementia caused by AD from other dementias.

- The ultimate goal of research is to uncover a serum biomarker that can identify patients in the preclinical/prodromal stage of AD, so that disease-modifying therapies and preventive measures can be initiated before symptoms manifest.

- Science is a long way from making this goal a reality, but recent changes in the diagnostic criteria for AD will encourage research in this area of study.

Bottom Line

Researchers are working to uncover biomarkers that will identify patients in the preclinical or prodromal stage of Alzheimer's disease, but diagnosis remains clinical. Recent changes to diagnostic criteria will encourage research in this area.

References

1. Jack CR Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):257-262.
2. 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(3):263-269.
3. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of 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(3):280-292.
4. 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(3):270-279.
5. Cummings JL. Biomarkers in Alzheimer's disease–perspectives for the future. US Neurology. 2010;6(1):23-27.
6. Sperling R, Keith J. Biomarkers of Alzheimer disease: current and future applications to diagnostic criteria. Continuum (Minneap Minn). 2013;19(2 Dementia):325-338.
7. Craig-Shapiro R, Fagan AM, Holtzman DM. Biomarkers of Alzheimer's disease. Neurobiol Dis. 2009;35(2):128-140.
8. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010;9(1):119-128.
9. Foster NL, Heidebrink JL, Clark CM, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain. 2007;130(pt 10):2616-2635.
10. National Coverage Determination (NCD) for FDG PET for Dementia and Neurodegenerative Diseases (220.6.13). Centers for Medicare and Medicaid Services. http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=288&ncdver=3&bc=BAABAAAAAAAA&. Accessed May 9, 2014.
11. Small GW, Bookheimer SY, Thompson PM, et al. Current and future uses of neuroimaging for cognitively impaired patients. Lancet Neurol. 2008;7(2):161-172.
12. Clark CM, Schneider JA, Bedell BJ, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA. 2011;305(3):275-283.
13. Johnson KA, Minoshima S, Bohnen NI, et al. Update on appropriate use criteria for amyloid PET imaging: dementia experts, mild cognitive impairment, and education. Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. Alzheimers Dement. 2013;9(4):e106-e109.
14. AMYViD [package insert]. Indianapolis, IN: Eli Lilly & Co; 2012.
15. First guidelines published for brain amyloid imaging in Alzheimer's. Alzheimer's Association. http://www.alz.org/news_and_events_60578.asp. Published January 28, 2013. Accessed May 9, 2014.
16. Zakaib GD. FDA approves Amyvid for clinical use. Alzforum. http://www.alzforum.org/news/research-news/fda-approves-amyvid-clinical-use. Published April 9, 2012. Accessed May 16, 2014.
17. Skillbäck T, Zetterberg H, Blennow K, et al. Cerebrospinal fluid biomarkers for Alzheimer disease and subcortical axonal damage in 5,542 clinical samples. Alzheimers Res Ther. 2013;5(5):47.
18. Irizarry MC. Biomarkers of Alzheimer disease in plasma. NeuroRx. 2004;1(2):226-234.
19. Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med. 2012;367(9):795-804.
20. Bertram L, McQueen MB, Mullin K, et al. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. Nature Genetics. 2007;39(1):17-23.
21. Strittmatter WJ, Roses AD. Apolipoprotein E and Alzheimer's disease. Annu Rev Neurosci. 1996;19:53-77.