... ALZHEIMER DISEASE

Biomarkers and gene mutations as aids for detecting AD early

Alzheimer disease (AD) is the most common form of dementia, accounting for 50% to 56% of all dementias, and is marked by slow, progressive cognitive and behavioral decline along with prominent memory dysfunctions. Advancing age remains the greatest risk factor for AD, followed by family history. The clinical manifestations of AD result from a loss of neurons and synaptic connections and the shrinkage of large cortical neurons. These pathologic consequences lead to gross cortical atrophy with associated sulcal widening, gyral atrophy, thinning of the cortical ribbon, and compensatory ventricular dilatation, all of which can be seen on MRI studies obtained later in the course of the disease. Current therapies for Alzheimer disease variably slow its progression but do not cure the underlying pathology. Typically, treatment is initiated after significant cortical atrophy has already occurred.

The ability to diagnose AD before symptoms occur would allow patients to seek medical treatment earlier in the disease course or even based simply on family history. New discoveries involving amyloid and tau neuropathology as well as neurogenetics could make this possible. Today, biomarker studies using cerebrospinal fluid (CSF) are the most direct means to study the progression of AD; they are useful in detecting preclinical symptomatic stages of the disease and are much more sensitive than some of the earlier disputed single-center studies. Patients who are concerned about developing Alzheimer disease will undoubtedly come into contact with information about CSF biomarkers and will have questions for their primary care providers. Therefore, when primary medical providers, including physician assistants, are taking a detailed family history, it is imperative that they understand the significance of these biomarkers and neurogenetics.

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»NEUROGENETICS IN ALZHEIMER DISEASE

Family history is the second greatest risk factor for developing AD. Three gene mutations have been identified that are known to be involved in early-onset familial Alzheimer disease: amyloid precursor protein (APP) on chromosome 21, presenilin 1 (PSEN1) on chromosome 14, and presenilin 2 (PSEN2) on chromosome 1. The discovery of these mutations is crucial because a heritability study demonstrated that up to 80% of the variability in AD is related to genetics whereas only 20% is related to environmental factors. Commercial testing is available for these three gene mutations for patients with strong family histories of Alzheimer disease. However, because not all the genes involved in AD have been identified, there is potential for false-negative findings in patients who have a positive family history.

Genetic testing is not routinely recommended. However, a referral for genetic counseling is appropriate in patients with a strong family history of AD or evidence of family members who have documented APP, PSEN1, and/or PSEN2 mutations. Therefore, clinicians must dig a little deeper when asking patients about their family history of AD. Ask if a family member with AD had genetic testing done or if AD was confirmed postmortem. This may help clinicians avoid making a misleading diagnosis.

»CSF BIOMARKERS: NEW TOOLS FOR THE EARLY DIAGNOSIS OF AD

Beta-amyloid protein

It has been well-established that neuritic plaques, which are pathognomonic for AD, contain beta-amyloid protein (Aβ). However, research suggests that Aβ peptides are normal products of cellular metabolism where different isoforms of Aβ exist. These isoforms are known to be 40 to 42 amino acid peptides long, with Aβ12 being the more toxic isoform. The accumulation of these peptides is believed to initiate the pathogenesis of Alzheimer disease. In addition, experts no longer believe this accumulation is caused merely by the overproduction of these proteins but rather by an imbalance in the production and clearance of these peptides.

Tau protein

Neurofibrillary tangles (NFTs) are another histologic landmark of Alzheimer disease. NFTs are intraneuronal cytoplasmic inclusions of abnormally accumulated hyperphosphorylated tau. Tau is a naturally occurring axonal protein that is known to be associated with microtubule binding and stabilization. NFT formation first occurs in the transentorhinal cortex during the early progression of AD and is well-correlated with specific defects in memory loss. The entorhinal cortex is where sensory information from the neocortex interfaces with the hippocampus. Newer research confirms that selective vulnerability exists in the neurons in layer II of the entorhinal cortex that is associated with AD. Today, biomarker studies using cerebrospinal fluid (CSF) are the most direct means to study the progression of AD; they are useful in detecting preclinical symptomatic stages of the disease and are much more sensitive than some of the earlier disputed single-center studies. Patients who are concerned about developing Alzheimer disease will undoubtedly come into contact with information about CSF biomarkers and will have questions for their primary care providers. Therefore, when primary medical providers, including physician assistants, are taking a detailed family history, it is imperative that they understand the significance of these biomarkers and neurogenetics.

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with the earliest regional atrophy in the brain during the development of AD.  

Commercially available CSF test Cerebrospinal fluid testing is useful in detecting the preclinical and symptomatic stages of AD. One physiologic reason is because CSF is present not only in the spinal cord but also in the subarachnoid space and ventricular system, which allows direct access to several regions of the brain involved in AD. A CSF profile suggestive for AD includes low Aβ42 levels and high CSF tau concentrations, but other forms of dementia such as frontotemporal dementia share the same profile. However, new discoveries in the clinical science of biomarkers may be able to assist in differentiating between AD and other forms of dementia. Some of these new discoveries focus on the ratio of some of the Aβ isoforms instead of just the isoforms themselves, such as the Aβ42/Aβ40 ratio. Research indicates that patients with an AD diagnosis have a pronounced decrease in the Aβ42/Aβ40 ratio. Therefore, CSF testing may be more useful than previous tests at aiding in the early diagnosis of AD as well as in clinical phases of the disease. In addition, increases in Aβ42 and Aβ16 (a short truncated isoform) were found to accompany Aβ42 decreases in CSF, but no conclusive studies have been completed to justify their use in the early diagnosis of AD.

TAKE-HOME POINTS

■ In patients with AD, significant cognitive decline occurs before amyloid plaques and neurofibrillary tangles (NFs) begin to form, and significant cortical atrophy takes place before treatment is typically initiated. Therefore, earlier diagnosis and referral is more crucial than ever.

■ Neurogenetic susceptibility may account for most of the variability in the development of AD, and three key mutations have been found to be associated with the development of AD: APP, PSEN1, and PSEN2.

■ Aβ peptides are naturally occurring metabolic products, with Aβ42 being much more prevalent than the aggregation-prone and toxic Aβ40 isoform. Low levels of CSF Aβ42 are found in AD and other dementias, but the decrease in the Aβ42/Aβ40 ratio has been found to be more sensitive in patients with AD.

■ Neurofibrillary tangles are seen in AD, specifically in the transentorhinal cortex, which has been correlated to specific memory loss. High total tau is found in the CSF of patients with AD and other forms of dementia. However, p-tau assays can discriminate AD from other forms of dementia.

■ The primary health care provider should consider a referral for genetic counseling or an earlier neurology consultation in asymptomatic patients concerned with developing AD and in those who have a family history of more than one direct family member with AD or a family member with documented mutations or confirmatory CSF profiles.

High total tau (t-tau) concentrations in the cerebrospinal fluid are well-correlated with an AD diagnosis. However, the presence of a high t-tau concentration in the CSF profile cannot differentiate between other forms of dementia such as vascular dementia. Newer studies have confirmed that hyperphosphorylated tau (p-tau) assays can distinguish Alzheimer disease from other forms of dementia and are far more specific and sensitive than using CSF concentrations of t-tau or Aβ42.

CHANGING THE WAY CLINICIANS DIAGNOSE AD When taking a family history, clinicians can no longer merely document whether a family history of AD exists. With these new breakthroughs, it is now necessary to dig a bit deeper and document whether those identified family members underwent genetic testing, if they had positive mutations of APP, PSEN1, and/or PSEN2, and if they had CSF biomarker assays that were suggestive of AD. The primary health care provider should request a referral for genetic counseling or an earlier neurology referral in patients with a family history significant for a suggestive CSF test result and/or for APP, PSEN1, and/or PSEN2 mutations in patients who have concerns about developing AD but are not exhibiting signs or symptoms. Whereas in the past, clinicians chose to wait for these patients to develop signs or symptoms of Alzheimer disease before initiating treatment or referring them to a neurologist, this standard of care is no longer acceptable. Even if no reported family history of genetic testing or CSF marker testing is present, clinicians can help make a significant difference in the outcomes of patients who have more than one or two direct family members with AD by initiating genetic counseling or referring them to a neurologist who specializes in dementia earlier to determine if or when this type of testing should be done.

REFERENCES