Memory Care Monthly

Supporting Healthcare Professionals in Caring for the Aging January 2007

New Year's Resolution: Detect Alzheimer's Early

With the recent consensus report that treatment of Alzheimer's Disease (**AD**) with cholinesterase inhibitor therapy most likely delays disease progression [Geldmacher et al. J Nutr Health Aging (2006) 10: 417-429], there is good reason to make early detection of memory loss a New Year's resolution. This resolution will be further rewarded with the next generation of soon-to-be available treatments—Flurizan and Alzhemed—that directly retard the pathophysiology of AD (excessive production and/or reduced clearance of beta amyloid).

The following summary is intended to serve as a practical approach to achieving the New Year's resolution of detecting AD early. For further information, please go to www.mccare.com.

1. **Why Bother Detecting AD Early?**
   a. Early detection, accurate diagnosis and proper treatment can delay AD progression for years.
   b. Doing so allows patients and families to better plan for the future.
   c. Doing so allows early diagnosis and treatment of non-AD disorders to minimize the degree to which they cause impairment.
2. **Who To Screen**
   a. All persons over 65 years old.
   b. Persons with evidence of or a complaint of decline in memory or other cognitive abilities.
   c. Persons with evidence of or a complaint of greater difficulty performing their most complex tasks.
3. **When To Screen**
   a. As part of the annual physical checkup for persons over 65 years old.
   b. At the time of the report of subjective decline in cognitive or functional abilities.
   c. Whenever evidence suggests that cognitive abilities are declining.
4. **How To Screen**
   a. The MCI Screen is an objective test that can be administered in 8 to 12 minutes in physician offices by an office assistant, and is 97% accurate in discriminating normal aging from early stage AD or a related disorder. The required training to administer the MCI Screen is brief and usually requires just 15-20 minutes of practice prior to reliable administration. Medicare reimbursement ranges from $120 to $200 and access to the MCI Screen is available at www.mccare.com.
   b. If the first option is not available, then patients can be referred to a neuropsychologist for testing.

5. **What To Do With The Screening Results**
    a. Normal MCI Screen Result
        i. If the result is normal, then there is a 97-99% chance that the patient does not have AD or a related disorder.
            1. *If the physician's judgment concurs with the "Normal" result, the patient can*:
                a. Do nothing at this time but be checked annually thereafter with the MCI Screen.
            2. *If the physician still suspects impairment, then*:
                a. Repeat the MCI Screen in two to four weeks. A normal result at this time greatly increases the certainty that the patient does not have AD or a related disorder.
                b. Proceed with a diagnostic evaluation if one is certain that the patient is impaired. See the Physician Report of the MCI Screen for specific diagnostic test recommendations.
    b. Abnormal MCI Screen Result
        i. If the result indicates impairment, then there is an 85-95% chance that the patient has AD or a related disorder.
            1. *Unless the reason for impairment is already known, further evaluation is indicated*. In this case, The Physician Report of the MCI Screen indicates the appropriate diagnostic lab and imaging studies to perform. The Patient Report provides educational material explaining the reasons for doing further evaluation. Proper evaluation yields approximately a 90% accuracy in correctly diagnosing AD.
            2. *If the physician strongly believes that the patient is not impaired, then*:
                a. Repeat the MCI Screen in two to four weeks to see if the first result was a false positive one.
                b. Repeat the MCI Screen in six to 12 months to see if there is any evidence of decline in the test's sub-scores.

Free Patient Brochures

Make sure your patients know that you now offer memory assessment services. We can send you complimentary copies of our educational patient brochure, **About Memory Loss**. To request copies, please send an email to customerservice@mccare.com and include the address to where you would like the brochures mailed.

EDUCATIONAL MATERIAL

Genetic Insight for Alzheimer's Disease

Previous research of genetically inherited forms of AD provided key evidence that a major aspect of AD pathophysiology arises from altered processing of the amyloid precursor protein (**APP**) to produce beta amyloid. More recently, genetic studies of families with early onset AD, in which the first symptoms appear between 30 and 55 years old, may identify novel AD therapies.

Presenilins 1 and 2

Presenilins 1 and 2 were the first mutations of gamma secretase that were found to produce early onset AD; presenilin 1 accounts for about 10% of all such cases. In normal aging individuals, gamma secretase cuts APP to produce a fragment that is not harmful and can be recycled. In families with the presenilin 1 or 2 mutation, the mutated gamma secretase cuts APP to produce the 42 amino acid fragment known as beta amyloid 1-42, which produces the full pathophysiology of AD.

There are an estimated 200-300 different gamma secretase mutations capable of producing early onset AD. Studies of families with early onset AD have also found mutations or duplicated segments of APP. The identification of the key sites on these mutated proteins has led to the synthesis of molecules targeted at these sites. These molecules may represent the most potent class of AD drugs because they are blocking the forms of AD with the most rapid pathophysiological progression and the earliest clinical manifestations.

Apolipoprotein E

The apolipoprotein E-mediated transport rate of LDL cholesterol into nerve cell membranes is key to AD pathophysiology, and the different alleles encoding apolipoprotein E (**ApoE**) are associated with substantially different rates of intracellular LDL transport. The ApoE e4 allele is the major genetic risk factor for the most common form of AD (so called sporadic or late onset AD) in which dementia usually begins after 65 years old (since mild cognitive impairment begins an average of 7 years before dementia onset, this means that AD-associated memory loss begins after age 58 years old). Between 40% and 60% of all late onset AD cases have an ApoE e4 allele. Persons 50 years and older have a 1 in 4 chance of having an ApoE e4 allele—a single e4 allele approximately triples AD risk and two e4 alleles increase AD risk by 5-9 fold.

ApoE binds to its receptor on nerve cell membranes and facilitates intracellular LDL cholesterol transport. LDL cholesterol binds to APP to facilitate APP cleavage at specific sites by secretase molecules. Intracellularly, LDL cholesterol facilitates alpha secretase to cleave APP at its alpha site. Outside of neurons, LDL cholesterol facilitates beta secretase to cleave APP at its extracellular beta site; gamma secretase then cleaves APP at its intra-membranous gamma site. The combination of beta followed by gamma secretase cleavage increases the likelihood that the resulting APP fragment will be beta amyloid 1-42, which initiates AD pathophysiology. Thus, the relative amounts of extracellular and intracellular LDL cholesterol play an important role in AD pathophysiology, with high levels of extracellular LDL cholesterol increasing AD pathology. The e4 ApoE product is much less efficient than the e2 and e3 ApoE products at transporting LDL cholesterol intracellularly, which results in a relative buildup of LDL extracellularly. This relative buildup of extracellular LDL cholesterol among ApoE e4 patients therefore increases beta amyloid production to increase AD pathology and risk. Persons with elevated blood levels of LDL cholesterol and the ApoE e4 allele presumably have even greater AD risk than patients with the ApoE e4 allele and normal LDL cholesterol blood levels.

Research Updates

Diagnosis: Researchers Identify Proteins That May Be Unique to Alzheimer's

The study conducted by scientists at Cornell University and Weill Cornell Medical College has identified 23 proteins in spinal fluid that may be unique to Alzheimer's disease (AD). These proteins may serve as a unique "fingerprint" that could one day lead to a test to diagnose AD. In this study, 2,000 proteins from 34 patients with autopsy-proven AD were compared to those of 34 age-matched controls without the disease. Researchers used proteomics methods, which analyzes proteins in the cerebrospinal fluid. This was the first study to use such methods to identify a small group of biomarkers.

Reference: Finehout et al. Annals of Neurology, December 2006; Vol 60 (Online Publication).

Diagnosis: Imaging Distinguishes Between Alzheimer's Disease, Mild Cognitive Impairment and Normal Aging

Researchers at the University of California Los Angeles demonstrated that FDDNP-PET can distinguish between subjects with Alzheimer's disease (AD), mild cognitive impairment (MCI) and no cognitive impairment. Currently definitive diagnosis of AD is made possible only at time of autopsy. Therefore, the findings of this study may have a significant impact on future AD diagnosis. Early and definitive diagnosis of the disease can aid in early treatment and delay its progression.

During this study, researchers followed 83 volunteers who had reported memory problems. Cognitive testing revealed that 25 had AD, 28 had MCI and 30 had no cognitive impairment. PET was performed on all subjects after injection of FDDNP, a fluorescent molecule that has previously been shown to bind to plaques and tangles. All volunteers also had FDG-PET scans and 72 had MRI. Global values for FDDNP bindings were significantly higher for those with MCI when compared to volunteers without impairment. Additionally, FDDNP binding was higher for those with AD compared to those with MCI. Furthermore, compared to the two other imaging techniques, FDG-PET and MRI, FDDNP-PET yielded the greatest diagnostic accuracy.

Reference: Small et al. NEJM (2006) 355: 2652-2663.

Dementia with Lewy Bodies: Worse Prognosis than Alzheimer's Disease

The study conducted by Galvin et al from Washington University School of Medicine, St. Louis, has shown that patients who have dementia with Lewy Bodies (DLB) have lower survival and more rapid progression than patients with Alzheimer's disease (AD). Researchers compared 315 participants (63 with DLB and 252 with AD) enrolled in a prospective longitudinal study of memory and aging with annual clinical and cognitive assessments and followed until death.

The risk of mortality was 88% higher among patients with DLB than those with AD although their rate of cognitive decline had no significant differences. Men with DLB had a 51% higher risk of mortality than women with DLB. The median survival after diagnosis was 7.27 years with DLB, and 8.47 years with AD.

Reference: Galvin et al. Neurology (2006) 67: 1935-1941.

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