Memory Care Monthly

Supporting Healthcare Professionals in Caring for the Aging May 2007

Disorders Associated with Cholinergic Deficit and Cognitive Impairment

The basal forebrain nuclei are the primary source of neurons that release acetylcholine. These cholinergic neurons send projections to most cortical areas as well as to the brainstem, thalamus and basal ganglia. Consequently, symptoms resulting from cholinergic deficit include brainstem abnormalities (altered breathing, dry mouth, reduced sweating, non-REM sleep, and tachycardia), thalamic abnormalities (confusion or disturbed attention), basal ganglia abnormalities (abnormal or uncoordinated movement) and cortical abnormalities (cognitive or functional or behavioral disturbances).

For the long term treatment of a patient with a suspected cholinergic deficit, it is useful to know that Exelon (rivastigmine) continues to inhibit cerebrospinal fluid acetyl- and butyryl-cholinesterase levels for at least one year[1]. This means that acetylcholine levels continue to be elevated so that a clinically beneficial effect can be sustained. In contrast, Aricept (donepezil) and Razadyne (galantamine) may upregulate acetylcholinesterase cerebrospinal fluid levels after one year of treatment[2, 3], which would lead to a loss of treatment effect. When a loss of treatment effect occurs with Aricept or Razadyne, there are two options: 1) Increase the dose; or 2) switch to Exelon.

Cholinergic neurons are more susceptible to damage by a variety of insults, possibly because they use acetyl-CoA not only to produce the cell's energy but also to make acetylcholine[4]. While Alzheimer's is the disease most commonly thought of with regard to cholinergic deficit, a large number of disorders can reduce brain acetylcholine that can clinically respond to cholinesterase inhibitor therapy. These disorders include:

CAUSES OF CHOLINERGIC DEFICIT AND COGNITIVE IMPAIRMENT

MEDICAL CAUSES

- Diabetes Mellitus Type II[5]
- Hypertension[6]
- Breast and Lung cancer[7]
- Hysterectomy/menopause with estradiol levels ≤ 20 pg/ml[8]
- Children with prenatal exposure to nicotine (25% of pregnant women smoke).[9]

IATROGENIC CAUSES

- Older antipsychotics, and atypical antipsychotics to a lesser degree.[10]
- Older Anticholinergics not specific for M3 muscarinic receptors[11]
- Tricyclic antidepressants [12]
- Anticonvulsants
- Benadryl (diphenhydramine)[13]
- Severe psychostimulant abuse[14]
- Radiation Therapy
- Chemotherapy
- Tamoxifen
- Irinotecan[15]
- Colchicine inhibitors of mitosis[16]

NEUROLOGIC AND PSYCHIATRIC CAUSES

- Alzheimer's Disease
- Cerebrovascular Disease[17]
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[18]
- Anterior Communicating Artery Aneurysm[19]
- Lewy Body Disease[20]
- Parkinson's Disease[21]
- Progressive Supranuclear Palsy[22]
- Epilepsy with Hippocampal Atrophy[23]
- Multiple Sclerosis[24]
- Traumatic Brain Injury[25]
- Schizophrenia[26]
- Moderate to severe inherited spinocerebellar ataxia[27]
- Depression unresponsive to 5HT and NE reuptake inhibitors
- Non-REM and REM Sleep Disorders [28]
- Alcoholism (basal forebrain nuclei)[29]

PEDIATRIC NEUROLOGIC CAUSES

- Down Syndrome[30]
- Huntington's Disease[31]
- Autism (basal forebrain nuclei)[32]
- Fragile X syndrome[33]
- Congenital Central Hypoventilation Syndrome (CCHS)[34]
- Rett Syndrome [35]
- Congenital ornithine transcarbamylase (OTC) deficiency[36]

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Product Enhancements: *Coming This Summer*

- **Administer the MCI Screen in Spanish.** We are in the process of adding a Spanish wordlist and Spanish instructions to the MCI Screen. Using this option, you will be able to administer the test in Spanish to your Spanish speaking patients.
- **Measure Treatment Effect and Cognitive Function.** In addition to the Overall Impression of the MCI Screen (Impaired vs. Normal), which we currently report, we will soon begin providing a quantitative measure of cognitive function. This measure will be useful for two reasons. First, it will enable you to track improvement or decline across successive tests. The second is to better understand the extent to which any given patient is either normal or impaired.
- **Streamlined Report.** Based on customer feedback, we will be offering a shorter report with each patient's results only. The additional information currently offered on the MCI Screen Report, such as the ADRD diagnostic guidelines and the references, will be available for printing if needed.

Biomarker for Advanced Alzheimer's Found in Patients with Mild Cognitive Impairment

A recent study found that the ratio of amyloid-beta and tau-proteins in the CSF of persons with mild cognitive impairment was the same as the ratio in patients with advanced Alzheimer's disease (AD). The study was led by Ann M. Fagan, PhD, from the Washington University School of Medicine in St. Louis, MO. In 139 subjects aged 60-91 and clinically judged as cognitively normal (Clinical Dementia Rating Scale [CDR]=0) or having very mild (CDR=0.5) or mild (CDR=1) AD dementia, CSF beta amyloid 40 ($A\beta_{40}$) and $A\beta_{42}$, tau, phosphorylated tau_{181}, and plasma beta $A\beta_{40}$ and $A\beta_{42}$ were measured and clinically followed up to 8 years. Both subjects with mild and advanced AD had reduced levels of CSF $A\beta_{42}$ and increased levels of tau and phosphorylated tau_{181}. CSF $A\beta_{42}$ levels corresponded closely with the presence or absence of brain amyloid when the subjects were examined with the Pittsburgh Imaging Compound (PiB) which binds to amyloid and can be detected by PET. CSF tau to $A\beta_{42}$ ratio and phosphorylated tau_{181} to $A\beta_{42}$ ratio accurately predicted conversion from normal to AD dementia. Reference: Fagan et al., *Arch. Neurol.*, 64(3), 343-9, 2007.

Structural Brain Changes Present 4 Years Before Diagnosis of Mild Cognitive Impairment

Charles D. Smith, MD at University of Kentucky Alzheimer's Disease Center (UK-ADC) found that patients classified as cognitively normal had structural brain changes such as decreased gray-matter volumes in the anteromedial temporal lobes bilaterally and in the left angular gyrus. These structural changes were present on average 4 years before diagnosis of mild cognitive impairment (MCI). The study included 136 subjects over the age of 65, all cognitively normal, participating in the Biologically Resilient Adults in Neurologic Studies (BRAINS) group, made up of very educated and motivated individuals representing the very healthy extreme. At baseline structural magnetic resonance imaging (MRI) was performed and the subjects were followed for 5 years. Furthermore the subjects underwent annual cognitive testing and semiannual medical examinations. At an average of 5.4 years of follow-up, 23 subjects had developed MCI and 9 of 23 had progressed to AD. Reference: Smith et al., *Neurology*, 68(16), 1268-73, 2007.

Type 2 Diabetics Have Increased Risk of Developing Amnestic Mild Cognitive Impairment

Jose J. Luchsinger, MD, from Columbia University Medical Center in New York City studied 918 individuals aged 65 years or older without mild cognitive impairment (MCI) or dementia. Baseline data were gathered between 1992 and 1994 and included in-person interview about general health and function, medical history, neurologic examinations and neuropsychological testing. The average follow-up period was 6.1 years and participants were assessed every 18 months until 2003. During this period 334 had developed MCI with 160 being amnestic cases while the remaining 174 nonamnestic. Analysis of data showed related to a significantly higher risk of all-cause MCI and amnestic MCI (8.8%) after adjustment for all covariate. Diabetes was also related to a higher risk of nonamnestic MCI, but this association was appreciably attenuated after adjustment for socioeconomic variables and vascular risk factors. Reference: Luchsinger et al., *Arch. Neurol*., 64(4), 570-5, 2007.

Cyproterone More Effective in Curbing Aggression in Alzheimer's Patients than Haloperidol

Dr. Huertas of University of Alcala, Madrid, and colleagues studied 27 elderly patients with mean age of 80.7 years with Alzheimer's disease and related aggressive behaviors. Each patient underwent a 15-day washout for psychotropics, and then randomized and received either cyproterone 100mg per day or haloperidal 2 mg per day. After 90 days, 9 (69.2%) of the cyprotrone patients achieved complete elimination of aggression compared to only 2 (14.2%) individuals in the haloperidol group. Furthermore, 10 (71.4%) taking haloperidol had adverse events, compared with 4 (30.7%) taking cyproterone ($p = .035$). Reference: Huertas et al., *J. Clin. Psychiatry*, 68(3), 439-44, 2007.

Treatment with Galantamine Reduces Verbal Repetition in Alzheimer's Patients

Verbal repetition is a common symptom in patients with Alzheimer's disease (AD) and is effectively treated with galantamine, according to a recent study. Dr. Kenneth Rockwood, of Dalhousie University, Halifax, Nova Scotia, Canada and colleagues conducted secondary analysis of the Video-Imaging Synthesis of Treating Alzheimer's Disease study (VISTA), a 4-month, double-blind, randomized, placebo-controlled study of galantamine in 130 patients with mild to moderate AD. The Goal Attainment Scaling, in which individualized problems identified by patients/caregivers and treating physician, was assessed bimonthly as a primary outcome. Reduction of verbal repetition was set as a goal for 57 (44%) randomized patients. After 4 months, 58% of galantamine group and 24% ($p<0.01$) of the placebo group saw a reduction of verbal repetition. This reduction correlated with improvement in clinical measures, but not in standardized ones. Reference: Rockwood et al., *Neurology*, 68(14), 1116-1121.

Increase in Systolic Blood Pressure Increases Risk of Stroke in all Populations

Data from the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study was analyzed by Dr. David W. Brown and colleagues from Centers for Disease Control and Prevention in Atlanta, Georgia in an effort to investigate whether various blood pressure parameters helped prevent stroke. The analysis included 3295 men and 3462 women with median follow-up of 15 years. 113 fatal strokes occurred during this time period. The researchers concluded that for every 10 mm Hg increase in systolic blood pressure, the relative risk of stroke was 1.19 for men, 1.15 for women, 1.17 for whites, and 1.28 for African Americans. Reference: Brown et al., *Am. J. of Hypertens*., 20(3), 338-41, 2007.

Risk Factors for Stroke in Type 2 Diabetics Identified

Although type 2 diabetes mellitus (DM) is a strong predictor of cerebrovascular disease, few studies have assessed the incidence of stroke and the role of other risk factors in patients with type 2 DM. Italian researchers led by Dr. Carol Bruno Giorda from the Metabolism and Diabetes Unit in Chieri followed, over a 4-year period, 14,432 type 2 DM patients aged 40 to 97 years, with and without cardiovascular disease. The study found that prior history of stroke more than doubled the risk of stroke. Additionally, history of cardiovascular disease also increased risk of stroke as did age. In men without cardiovascular disease, HbA1c and smoking were predictors of stroke. In men with cardiovascular disease, predictors of stroke included: insulin therapy plus oral agents, treatment for high cholesterol, and low HDL cholesterol. In women, the risk factor for stroke that was identified was microvascular complications. Reference: Giorda et al. *Stroke*, 38(4), 1154-60, 2007.

Behavioral and Language Difficulties Distinguish Between Dementing Disorders

In the early stages of Alzheimer's disease (AD) and frontotemporal labor degeneration (FTLD) it may be difficult to differentiate these two disorders. Dr. Liscic and colleagues from the Washington University School of Medicine in St. Louis evaluated the clinical findings of autopsy-proven 48 FTLD and 27 AD patients, and found behavioral and language difficulties can distinguish between dementia due to FTLD and AD. According to this study, behavioral and language problems particularly impulsivity (P<.001), disinhibition (P<.001), social withdrawal (P = .01), and progressive nonfluent aphasia are more common in FTLD patients. Reference: Liscic et al., *Arch. Neurol.*, 64(4), 535-40, 2007.

Fish Oil May Slow Cognitive Decline

Two prospective studies link delay in progression of cognitive decline in elderly to intake of components of fish oils. In the first study, researchers evaluated n-3 highly unsaturated fatty acids (HUFAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and their effect on cognitive decline. Dr. Bouke Maria van Gelder, from National Institute for Public Health and the Environment in Bilthovern and colleagues evaluated data from 210 healthy men in the Zutphen Elderly Study, aged 70 to 89 years old in 1990. The diets of the subjects were assessed in 1990 and cognitive function was tested in 1990 and 1995. At baseline, all subjects had normal mental function and Mini-Mental State Exam (MMSE) scores were similar for all regardless of intake of EPA and DHA. In 1995 those who did not have an intake of EPA and DHA scored on average 1.2 points lower on the MMSE. Those in the lowest tertile of EPA and DHA intake had an average 1.1 lower score than those in the highest tertile. The researchers recommend a daily dietary intake of 400mg of EPA and DHA found in fish, meat, eggs, leeks, and cereal products.

The second study was led by Dr. Mary A. Beydoun, at the University of North Carolina in Chapel Hill. The researchers evaluated the link between concentrations of fatty acids in plasma cholesteryl ester and phospholipids and analyzed data from the Atherosclerosis Risk in Communities (ARIC) study which began in 1987. The study cohort included 2251 subjects aged 50-65 years at baseline. From 1987 through 1989, the Atherosclerosis Risk in Communities (ARIC) Study analyzed plasma fatty acids in cholesteryl esters and phospholipids in whites residing in Minneapolis, MN. From 1990 through 1992 and from 1996 through 1998, 3 neuropsychological tests in the domains of delayed word recall, psychomotor speed, and verbal fluency were administered. Among 2251 subjects, the risk of global cognitive decline increased with elevated palmitic acid in both fractions and with high arachidonic acid and low linoleic acid in cholesteryl esters. Higher HUFAs reduced the risk of decline in verbal fluency, particularly in hypertensive and dyslipidemic subjects. No significant findings were found for psychomotor speed or delayed word recall. References: van Gelder et al., *Am. J. Clin. Nutr.*, 85(4), 1142-7, 2007. Beydoun et al., *Am. J. Clin. Nutr.*, 85(4), 1103-11, 2007.

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