ALZHEIMER'S DISEASE COOPERATIVE STUDY

HBA PARTICIPANT NEWS

The Journal for Participants in the Home-Based Assessment Trial

Spring 2012

Exercise & Amyloid

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Greeting from the HBA Project Director

Dear HBA Participants,

Thank you to all of you who have completed the Retention Satisfaction Survey. You have given us invaluable feedback about your experience participating in the study. It is our honor to have you in this important study. Please know how much we appreciate you.

We are not done yet but the HBA study has taught us a great deal, both on where we are succeeding and where we need to improve in future studies of this type. For example we learned that we need to do more training with you, our study participants, at the beginning of a study like this. Unfortunately we learned that the equipment and the assessment frequency can lead people to drop out of the study early. We wish we had known this before so we could have prevented people from dropping out but we don't view this as a negative because it helps us understand what we can do to improve a study's design.

On the positive side we learned that cognitive and functional assessments of the type we are using in the HBA study do in fact demonstrate a way to observe and assess cognitive changes over time. These instruments, the phone, computer kiosk and mail-in questionnaire are showing us changes in a person's cognition as well as changes in a person's daily activities and functionality. These changes and being able to understand them are what we were hoping to see in this study. We look forward to learning more in the future as we continue the study to its end.

Speaking of the study's end, the last participant will exit the study in July 2013. Back when we started this seemed like such an unfathomable date of the distant future. Now it is nearly on our doorstep. We look forward to the study's end and to conducting the crucial analysis that will tell how the instruments used in the study can be used to help researchers assess various changes in people with memory concerns. With your help we will be able to assist researchers in their ongoing effort to find new and better ways to assess cognitive and functional decline.

Once again, you have my greatest appreciation for the time you have put into the HBA study and your continuing participation. To all of the research participants who contribute their time and energy to this project, thank you. Together we can make great strides in Alzheimer's research.

Mary Sano, Ph.D
HBA Project Director
Director, Mount Sinai Alzheimer's Disease Research Center

Home-Based ASSESSMENTS

Exercise & Amyloid

By Michael Rafii, MD, PhD

A sedentary lifestyle is associated with greater brain amyloid deposition among cognitively normal individuals with the E4 version of the apolipoprotein E (APoE) gene, according to a report published in the Archives of Neurology.

To examine the association between exercise and brain amyloid deposition among patients with and without the APoE4 allele, Denise Head, Ph.D., and colleagues from Washington University in St. Louis, tested for the APoE gene and administered a questionnaire on physical exercise engagement over the last decade to 201 cognitively normal adults (135 women) age 45 to 88 years. Samples of cerebrospinal fluid were collected from 165 participants and brain amyloid imaging was performed on 163 patients. Fifty-six of the volunteers, of various ages and both sexes, turned out to be positive for APoE4.

APoE4 gene carriers mitigated their inherited risk for developing Alzheimer's with frequent aerobic exercise

Patients who reported higher amounts of exercise had lower average levels of brain amyloid than did patients who reported lower amounts of exercise. Participants who were positive for the APoE4 gene had higher levels of brain amyloid compared with individuals negative for APoE4 gene.

The authors observed a novel interaction, such that a more sedentary lifestyle was associated with an even greater brain amyloid level in APoE4 carriers than for noncarriers. That is, those subjects with the APoE4 variant who rarely or never exercised had the most plaques, putting them at heightened risk for the memory loss of Alzheimer's disease. Interestingly, the carriers of the APoE4 gene who reported walking or jogging for at least 30 minutes five times a week had plaque accumulation similar to that of subjects who were APoE4-negative. In essence, the APoE4 gene carriers mitigated their inherited risk for developing Alzheimer's with frequent aerobic exercise.

From previous studies we know that APoE4 status is associated with an increased risk of cognitive decline and elevated amyloid deposition. In contrast, exercise has been associated with reduced risk of cognitive decline and lower levels of amyloid deposition. This data suggests that exercise at levels recommended by the American Heart Association may be particularly beneficial in reducing the risk of brain amyloid deposition in cognitively normal APoE4-positive individuals. This study is yet another example of how genetics interact with environmental influences to affect risk of manifesting a particular disease. A randomized clinical trial of exercise in cognitively normal individuals will help answer this question more fully, and lead to an intervention that can potentially alter disease progression.

Weight Change & Cognitive Function:
Results from the Women's Health Initiative

By Neelum T. Aggarwal, MD
Steering Committee Member, ADCS, Rush Alzheimer's Disease Center

It is very rare in the course of a community talk on lifestyle factors and their relation to cognitive function, that I don't discuss the "Big 3" - hypertension, diabetes and obesity. Some studies have suggested that dementia risk is greater in those who are obese. Other studies have suggested central adiposity may be protective against cognitive impairment and dementia in older women while others have suggested that lower weight may be associated with greater cognitive decline. In a recent article from Driscoll and colleagues, the authors attempted to characterize the relationship between changes in weight and waist circumference with cognitive function.

A total of 2238 women participating in the Women's Health Initiative (WHI) were followed longitudinally, in a sub-study called WHISCA (Women's Health Initiative Study of Cognitive Aging). The women enrolled in this study underwent detailed cognitive assessments, anthropometric measurements [weight, height, waist circumference, waist/hip ratio] and questionnaires regarding caloric intake using a Food Frequency Questionnaire. Other demographic characteristics that were assessed were level of education, cardiovascular risk factors [hypertension, smoking, history of stroke, heart disease, diabetes, alcohol intake] and depression. Cognitive tests measured global cognitive function, verbal and figural memory, attention and working memory, spatial ability and fine motor speed. Other variables assessed were race, education in yrs (range 0-30), and the history or presence of medical conditions (heart disease, TIA, stroke, hypertension, diabetes, and Parkinson's disease).

At each WHI visit, staff obtained measurements of height and weight to calculate BMI, and also filled out a food questionnaire. Waist circumference was measured at baseline and year one. The investigators had measurements through the WHI follow-up and before entry in to WHISCA. Those who gained weight occurred more in younger women, those who were smokers at baseline, those who had lower waist/hip ratios and no hypertension. When the women were grouped according to weight gain, (>5% gain), weight lost (>5% loss) or remaining stable before enrollment, women with prior weight loss had a slightly lower cognitive score compared to women who had stable weight or those who had gained weight. When weight was grouped according to either any weight loss (<10% or >10%) or weight gain (<10% or >10%), women with >10% weight loss performed significantly worse on cognitive tests, than both weight gain groups, and those with 10% weight loss performed significantly worse than women gaining <10%.

At the time of WHI enrollment, 10.6% of women reported that they were currently following a low calorie diet. A low calorie diet was associated with lower cognitive test scores for attention and working memory ($p<0.001$) and higher scores on fine motor speed. Self report food intake measured by the food frequency questionnaire, revealed that higher caloric intake was associated with better cognitive performance.

This study examined the association of weight gain/loss to cognitive function, in a large group of older women. The results suggest that there were no differences in cognitive performance between women who gained weight or whose weight remained stable over approximately 3.5 years. Worse cognitive performance was associated with weight loss, and this relationship was not modified by initial BMI. The findings from this study are provocative, as they add to the literature that suggests weight loss could potentially signal the beginning of cognitive decline and dementia, and that there is no specific evidence to suggest a relationship between obesity and cognitive decline. The major limitation of this study as suggested by the authors was that it was done in women only, thus not generalizable to a general population of men and women. Unfortunately, this study only included ~10% of minority women in the sample, and thus was not able to comment on any differential findings that may have been influenced by race/ethnicity. Additional longitudinal studies to confirm these associations are needed, and could shed light on potential mechanisms of how body weight is associated with cognitive function.

Alzheimer's 2011: The Year in Review

By Michael Rafii, MD, PhD

This year we saw the publication of new diagnostic guidelines for AD formulated by committees sponsored by the National Institute on Aging and the Alzheimer's Association. The NIA/AA also published guidelines for diagnosis of mild cognitive impairment due to Alzheimer's disease, and for preclinical AD. These guidelines will be important tools for clinicians to diagnose AD in its earliest stages, and represent the first revision in 25 years.

An FDA advisory committee gave preliminary approval of the PET amyloid imaging ligand AV-45, citing work to be done to ensure consistency in reading PET scans. Full approval is expected sometime in 2012, if a uniform training program is implemented for radiologists interpreting the scans.

The European Medicines Agency announced the likely approval of hippocampal atrophy as a marker of early AD for the purpose of clinical trials. Much work has gone into linking hippocampal atrophy visualized by MRI, as an early and specific biomarker of neurodegeneration seen in AD.

IGAP—the International Genomics of Alzheimer's Project, a transatlantic collaboration to create the most detailed map of genetic variants that link to AD was also launched in 2011. Meta analysis of genome-wide association studies (GWAS) revealed four new genetic risk variants for AD.

In terms of clinical trials, Gantenerumab, an antibody against beta-amyloid, was shown to clear plaques when given intravenously, according to results from a Phase 1 trial. The drug seems to be one of the most potent developed thus far in reducing plaques. A Phase 2 gene therapy trial for Parkinson's disease was deemed a success. A similar Phase II gene therapy trial for AD, called the Nerve Growth Factor Study, is currently ongoing and recruiting. Multiple clinical trials, including the ADCS Phase III Resveratrol and Roche Phase II Gantenerumab trial are launching in 2012.

A very important paper by the Holtzman group at Washington University further established the relationship between ApoE4 genotype and decreased clearance of beta-amyloid from brain, both in humans and animal models. The idea that ApoE4 is less effective in removing beta-amyloid from the brain is not necessarily novel, per se, and had been previously shown. However, it had never been proven so convincingly and in such a complete manner in humans and animal models of AD. Together, the data suggest that ApoE variants contribute to a person's risk for AD by affecting the clearance of beta-amyloid from the brain long before amyloid plaque deposition begins. Later in the year, the same group reported that, in mice, lowering the levels of ApoE4 results in fewer amyloid plaques. The results imply that ApoE-lowering treatments have a place among proposed AD therapies, including immunotherapy, gene therapy, as well as beta-, and gamma-secretase inhibitors.

Results published in the Journal of the American Medical Association showed that women with sleep-disordered breathing (SDB)—pauses in breathing or reduced ventilation quality during sleep—are more likely to develop cognitive impairment five years later. The biology behind this finding may include hypoxia, or decreased oxygen delivery to certain parts of the brain, including the hippocampus which is critical in memory function. In addition, sleep fragmentation, which can interfere with memory consolidation, which occurs during certain stages of sleep, may also lead to cognitive problems. This study has really brought much needed attention to the evaluation of sleep as part of the work-up in individuals with Mild Cognitive Impairment.

We anticipate further progress in understanding the progression of the earliest stages of Mild Cognitive Impairment and AD with the Alzheimer's Disease Neuroimaging Initiative (ADNI2), The Dominantly Inherited Alzheimers Network (DIAN) study and the Alzheimer's Prevention Initiative (API) during 2012.

RESEARCH **ROUNDUP**

By Michael Rafii, MD, PhD
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Highlights From the 4th Annual Conference on *Clinical Trials in Alzheimer's Disease* (CTAD)

Held in San Diego, California, the venue was filled beyond capacity, drawing over 500 researchers from around the world. For the bulk of the meeting, researchers worked on methods they hope will improve future trials' chances of success. Clearly, better drugs are needed to treat AD, and there have been no drugs approved in over a decade. These methodological improvements include using more advanced statistical methods to analyze subject data, and to incorporate biomarkers of disease, including brain amyloid levels and measures of brain atrophy, as part of efficacy measures. In addition, there was much discussion on trial designs that target the disease in the pre-dementia phase of Alzhiemer's disease, sometimes referred to as Mild Cognitive Impairment (MCI).

Paul Aisen, MD, the Director of the ADCS at UC San Diego, opened the conference with a discussion of the evolution of AD trials and with a particular emphasis on why recent trials have failed. "The problem is we've tried to move from short acting to disease modifying drugs, and that's what has caused us to stumble," he said. "If interventions are needed before the brain has suffered significant damage and cognitive impairment, clinical trial design will require the detection of subtle and discreet changes, over long periods of time, and in large numbers of subjects."

There is international consensus that Alzheimer's disease starts some 15 years before symptoms of dementia appear, and new trial designs will need to be based on a biomarker-supported diagnosis of prodromal AD. Prodromal AD, which is the cause of cognitive impairment in roughly half of patients diagnosed with MCI, is basically defined as patients who are not demented but are destined to develop dementia within a few years because they have the earliest signs of AD developing in their brain. Several companies have begun using such designs to treat patients with prodromal AD, before dementia sets in.

Right Drug, Right Target, Right Time

"Ultimately, the challenge ahead requires increasingly sophisticated procedural, scientific and regulatory coordination between and among the private sector, the government and academia. Figuring out primary, secondary and tertiary prevention will require the right target at the right phase and right time" said Aisen.

Nevertheless, Aisen's confidence in collaborative approaches to AD research continues to grow. "Over the last few years I believe that the extent of precompetitive cooperation among companies, coupled with the cooperation among academics internationally, as well as government entities, has resulted in workable solutions to the difficulties of conducting trials in AD."

Detecting Early Changes

Traditional measures of cognition are not sufficiently sensitive to detect early, preclinical AD. Thus, efforts are underway to develop neuroscience-based cognitive assessments that are sensitive to subtle brain dysfunction. Diana Woodruff-Pak, Ph.D, of Temple University presented data suggesting that assessment of eyeblink conditioning may be useful in detecting early cognitive dysfunction in normal elders.

The test is non-invasive, relatively quick, and easy to administer. "It's simple...and studies have shown that the delayed eyeblink conditioning response is severely impaired in mild to moderate AD. This effect is specific to AD. Our hypothesis is that it detects changes in neural circuits and will prove to be useful as an initial screen for prodromal AD in normal population" said Woodruff-Pak.

A group led by Jacob Raber, Ph.D, of the Oregon Health and Science University, developed human versions of spatial navigation and object recognition tests commonly used in animal studies. These behaviors are sensitive to dysfunction in an area of the brain called the entorhinal cortex, which is affected early in AD. Raber's tests, called Memory Island and NINL (novel image, novel location), have both been shown to

Do you have a friend or family member who is interested in participating in an AD research study? If so, information on research studies can be found at www.adcs.org/Studies/clinalResearchStudy.aspx.

be sensitive for assessing cognitive performance and age-related cognitive decline in preclinical AD. The NINL test has even been shown to detect the subtle cognitive effects in individuals who are ApoE4-positive, which places them at elevated risk of developing AD.

Jeffrey Kaye, Ph.D, director of the Oregon Center for Aging and Technology (ORCATECH) at the Oregon Health and Science University discussed using unobtrusive home based monitoring to capture real-time continuous data for assessment of everyday cognitive change. A variety of sensors can track multiple behaviors and activities, including walking speed, medication adherence, and social activity, all of which are affected in the early stages of AD.

Preclinical AD: What We Know

As clinical trials edge toward prevention among people who are asymptomatic, it will be important to understand what characterizes people in the preclinical stages of AD. According to the recently proposed diagnostic criteria, preclinical AD can be divided into five stages depending on the presence of clinical symptoms, biomarkers of amyloid, and biomarkers of neuronal injury.

Ronald Petersen, MD, Ph.D, presented findings from the Mayo Clinic's Olmsted County Study of Aging, a population-based study of nearly 3000 non-demented elderly people. Complete evaluations on all of the subjects, including tests for subtle signs of cognitive impairment, found that among the nearly three-quarters of these subjects who were essentially "normal," more than half showed some signs of being on the pathway to AD. Petersen said these data indicate that the new pre-clinical AD criteria are able to identify individuals at very early stages on the AD pathway.

Society for Neuroscience, Washington, DC

With 42,000 members, the Society for Neuroscience's "Neuroscience 2011" meeting remains the largest meeting in the world on fundamental research on the nervous system. Many presentations were made with direct relevance to AD. One included the work of Dr. Gene Alexander from the University of Arizona, who found that physically fit seniors show fewer age-related changes in their brains. The findings further previous data in the AD field and underscore the importance of exercise for maintaining brain health throughout life.

As people age, some regions of the brain—including those responsible for attention and memory functions—begin to lose volume or shrink. To see how physical fitness affects brain aging and age-associated declines in cognition, Alexander and colleagues scanned the brains of 58 men and 65 women (ages 50 to 89 years) and evaluated their performance walking on an inclined treadmill.

The more physically fit a participant was, the fewer age-related brain changes they showed. In particular, exercise endurance and breathing efficiency offered the best combination of fitness measures in predicting patterns of brain aging. Individuals with higher levels of aerobic fitness also outperformed their less physically fit counterparts on tests measuring memory, executive function, and information processing. Identifying the fitness indices that are the best predictors of brain aging and cognitive performance may help improve exercise-based interventions to promote healthy brain aging.

Another interesting presentation was on how short-term estrogen treatment increases the volume of cortical gray matter in postmenopausal women. The research reveals a potential benefit from short-term hormone replacement therapy. Researchers, led by Paul Newhouse, MD, of Vanderbilt University, imaged the brains of 24 healthy postmenopausal women who took either estrogen or a placebo for three months. After treatment, the women who took estrogen had more gray matter in regions known to be involved in attention, decision-making, and memory.

The findings suggest the brain remains responsive to estrogen treatment even after menopause, and that this responsiveness or plasticity is important for preserving cognitive functioning, especially in the early postmenopausal period. The findings suggest that long-term hormone treatment, shown to have adverse effects on health in postmenopausal women, may be unnecessary for cognitive benefit. Short-term estrogen treatment in normal postmenopausal women is sufficient to increase gray matter in the brain.

HBA PARTICIPANT NEWS

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ALZHEIMER'S DISEASE ADCS COOPERATIVE STUDY

BRAIN EXERCISE

Mind Games are a really fun way to exercise the mind. Check out the mind games on the BrainBashers website — **www.brainbashers.com** — good for both caregivers who want to stay sharp and study participants with mild dementia.

Answer quickly. Starting with an empty barrel, which happens first?	What is represented by this BrainBat?	What four related words are merged here:
2/3 full 1/4 empty 1/2 full 3/4 empty	Schubert's Symphon	SWAS PURI UINM NTTU MGER MNER
3/4 empty: since 3/4 empty means 1/4 full.	Schubert's Unfinished Symphony	Spring, summer, autumn and winter

BRAINBASHERS™