

Memory Care Monthly

Supporting Healthcare Professionals in Caring for the Aging

November / December 2009

NEW YEARS RESOLUTION: RAISE AWARENESS ABOUT ALZHEIMER'S

As 2009 comes to a close and we look forward to 2010, we would like to reflect on the importance of increased Alzheimer's awareness. In that spirit, we are sharing with you the below article, originally written for National Alzheimer's Awareness Month, as part of a public education campaign about this terrible disease. We hope you will read it and share it liberally with any colleagues who might appreciate this important message.

Alzheimer's Awareness: Why Bother?

As you may have read elsewhere, November is National Alzheimer's Awareness Month. But surely, the public is already well aware of this horrible disease. After all, Alzheimer's has directly affected approximately 1 in every 2 families and the others must have certainly noted its prominent coverage in the news. We don't really need more awareness, right?

Wrong.

Some of the information below may surprise you. That is to say, it is information about which you are not presently aware. However, by merely learning the seven facts below you will be helping to reduce the Alzheimer's problem. That's right...making you aware of this information and encouraging you to share it with your social networks will facilitate a more informed and more effective approach to combating the threat we face from this disease.

First, here are a few facts and figures that you may already know. Alzheimer's currently affects more than 5 million Americans and that number is likely to triple by 2050. It is the sixth leading cause of death in the USA and is climbing steadily in the rankings. Also, Alzheimer's is the leading cause of dementia and accounts for about 65% of all dementia worldwide. These are all sobering facts but perhaps not new to your understanding.

7 Facts You Need To Know

Now, here are some points you may not know but should. It is the following information that I hope will stimulate discussion and promote a better understanding of the disease. With more discourse, we can begin to erode the lingering stigma that currently prevents some people with early symptoms from seeking timely medical attention.

1) We generally detect Alzheimer's at the end-stage of the disease.

On average, Alzheimer's follows a 14-year course from the onset of the first symptoms until death. There is some variability across patients but 14 years is pretty typical. The more surprising news is that, on average, we diagnose Alzheimer's in years 8-10 of that disease course. This means that for most patients, symptoms go undiagnosed and untreated for at least seven years, during which time the lesions spread through the brain and cause irreparable damage. **Please be aware that we diagnose Alzheimer's disease far too late to optimize the effects of currently available treatments.**

2) Memory loss is not a part of normal aging.

The point about end-stage detection raises an obvious question about "why" we diagnose this disease so late. There are many contributing factors but most of them can be reduced through awareness and education. Some patients resist medical attention in the early stages because they fear a stigmatizing label or because they are misinformed to believe that Alzheimer's cannot be treated. Many people, including a startling number of physicians, incorrectly believe that memory loss is a normal part of aging. Improving the timeliness of diagnoses for Alzheimer's is, in many ways, a problem that can be addressed through awareness and education. **Please be aware that memory loss is not a part of normal aging and, regardless of the cause of the memory loss, timely medical intervention is best.**

3) Current Alzheimer's drugs are probably more effective than you think.

Our widespread practice of late detection has many negative consequences. For example, one of the reasons that current treatments are often deemed ineffective is because they are routinely prescribed for patients with end-stage pathology who already have massive brain damage. With earlier intervention, treatment can be administered to patients with healthier brains, many of whom will respond more vigorously to the recommended therapy. Yes, we need better treatments, but a great start would be to intervene earlier with the treatments we already have. **Please be aware that currently approved treatments may be more effective than some headlines indicate.**

4) Alzheimer's disease can be treated.

Another treatment related concept about which everyone should be aware is this. Preventing or slowing further brain damage is preferable to letting the damage spread without constraint. Yet, many physicians, patients, and caregivers conclude that any treatment short of a cure is not worthwhile. While today it is true that we have no cure for Alzheimer's, that does not mean there is no treatment. With a good diet, physical exercise, social engagement, and certain drugs, many patients (especially those detected at an early stage) can meaningfully alter the course of Alzheimer's and preserve their quality of life. **Please be aware that "we have no cure" does not mean "there is no treatment".**

5) The Alzheimer's drug pipeline is full.

Here's another fact of which you should be aware. Through an intense research effort over the past twenty years, scientists have gained a lot of insight about Alzheimer's disease mechanisms and about other factors that increase the risk for the disease. Much has been learned and some very promising drugs, based on sound theoretical approaches, are in FDA clinical trials right now. While much of the disease remains shrouded in mystery and we may still be a long way from better treatments, it is possible that an effective agent is already in the pipeline. **Please be aware that, although we don't know when, better treatments for Alzheimer's are certainly on the way.**

6) Taking good care of your heart will help your brain stay healthy.

Know this; the health of your brain is very closely tied to the health of your body, particularly your heart. Researchers have shown conclusively that high cholesterol, high blood pressure, and obesity all confer greater risk for cognitive decline. The mechanisms that keep oxygen rich blood flowing through your body play a key role in maintaining a healthy brain. Everyone should be aware about the close association between vascular health and cognitive health. **Please be aware that maintaining good vascular health will help you age with cognitive vitality.**

7) Managing risk factors may delay or prevent cognitive problems later in life.

There are well-identified risk factors for Alzheimer's disease that are within our power to manage. These include diabetes, head injuries, smoking, poor diet, lethargy, and isolation. With greater awareness of these facts, we can imagine a world where diabetics take more care to control their blood sugar, where helmets are more prevalent in recreational activities that are likely to cause head trauma, where people smoke less and eat more fruits and vegetables, and where everyone makes a better effort to exercise and to stay socially engaged on a regular basis. While these facts may not be well known, they are all well proven. Galvanizing an effort to publicize them is one purpose of National Alzheimer's Awareness Month. **Please be aware that many risk factors for Alzheimer's can be actively managed to reduce the likelihood of cognitive decline.**

So why bother with Alzheimer's awareness? Because it is a terrible disease poised to ravage our aging society and the lack of education and awareness has led to a stigma that prevents a more proactive approach to early intervention. The result is that we diagnose it too late, which hampers the efficacy of available treatments. A more educated public could manage risk factors to minimize the likelihood of Alzheimer's, could monitor personal cognitive health with greater vigilance, and could seek medical attention at the earliest sign of decline. Physicians could then diagnose problems earlier and prescribe appropriate treatment including diet, exercise, and drugs to slow disease progression as much as possible. In the end, we could have fewer cases, more effective treatment, slower progression, higher quality of life, and lower healthcare costs. The social, emotional, and fiscal benefits of awareness and education in this area are too large to quantify.

By reading this article, you have increased your understanding of the problem and raised your awareness about what can be done. That is a great step in the right direction but you can do one thing more. You can help to spread this message.

In the spirit of National Alzheimer's Awareness Month, please share this article with your friends to promote more widespread awareness. Post it to your Facebook page, mark it in Delicious, Tweet it, Digg it, or email it. It doesn't matter how you do your part, it only matters that you get it done.

7 Facts to be Aware of:

1. We generally detect Alzheimer's at the end stage of the disease.
2. Memory loss is not a part of normal aging.
3. Current Alzheimer's drugs are probably more effective than you think.
4. Alzheimer's disease can be treated.
5. The Alzheimer's drug pipeline is full.
6. Taking good care of your heart will help your brain stay healthy.
7. Managing risk factors may delay or prevent cognitive problems later in life.

FEATURED ARTICLE

DIETARY PATTERN AND REDUCED RISK OF ALZHEIMER'S DISEASE

A new study has shown that a dietary pattern high in healthy fats (mono-saturated and omega-3 and omega-6 polyunsaturated fatty acid), folate, and vitamin E, and low in saturated fatty acids and vitamin B12 is associated with a reduced risk of Alzheimer's disease (AD). This study was presented at the 134th Annual Meeting of the American Neurological Association by Dr. Nikolaos Scarmeas and his colleagues from the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center.

In a community-based study of 2,148 non-demented participants ages 65 and older, 253 developed AD during a mean 3.9 years of follow-up. A reduced rank regression (RRR) analysis was used to determine linear combinations of 30 food groups that explained variation in seven nutrients potentially related to AD. Dietary information was gathered using the Willet's 61-item semi-quantitative food frequency questionnaire.

Researchers found that the AD protective RRR dietary pattern included "green food" such as salad dressing (olive oil and vinegar), nuts, fish, poultry, tomatoes, cruciferous vegetables (e.g. broccoli, cauliflower, Brussels sprouts, kale, and cabbage), fruits, and dark- and green-leafy vegetables. They also found that low consumption of "red food" such as high-fat dietary, red meat, organ meat, and butter was beneficial. When divided into 3 groups, those with the high and middle RRR pattern had 38 to 46 % and 19 to 27 % reduced risk of AD, respectively,

compared to the low RRR pattern.

The beneficial foods studied are similar to those found in a Mediterranean diet, but not identical, suggesting that a certain combination of food is associated with reduced risk for AD via a particular set of nutrients, and that other dietary combination may be also protective against AD.

Scarmeas N et al. The 134th Annual Meeting of the American Neurological Association.

RESEARCH UPDATES

DNA BETA-AMYLOID1-42 TRIMER IMMUNIZATION FOR ALZHEIMER'S DISEASE IN A WILD-TYPE MOUSE MODEL

Previously, a clinical trial in which patients with Alzheimer's disease (AD) were immunized with Abeta42 peptide, was discontinued due to severe adverse effects - meningoencephalitis occurred in 6 % of immunized patients - although follow-up of a few study patients showed that Abeta42 peptide immunization did indeed lead to a reduction in plaque load. This adverse effect may have been caused by the choice of QS21 as a T helper 1 cell (TH1)-type of adjuvant.

Dr. Doris Lambracht-Washington from Alzheimer's Disease Center, University of Texas Southwestern Medical Center and her colleagues have developed DNA Abeta42 trimer immunization to produce specific TH2-type antibodies to provide an effective and safe therapy for AD by reducing elevated levels of Abeta42 peptides that occur in the AD brain. In this study, they compared the immune response in wild-type mice after immunization with DNA Abeta42 trimer and Abeta42 peptide.

Wild-type mice received either 4 μ g of DNA Abeta42 trimer immunization administered with gene gun (n=8) or intraperitoneal injection of 100 μ g of human Abeta42 peptide with the adjuvant Quil A (n=8). Titers, epitope mapping, and isotypes of the Abeta42-specific antibodies were analyzed.

DNA Abeta42 trimer immunization resulted in antibody titer with a mean of 15 μ g per milliliter of plasma. The isotype profile of the antibodies differed markedly. A predominant IgG1 antibody response was found in the DNA-immunized mice, indicating a TH2 type of immune response (IgG1/IgG2a ratio of 10). The peptide-immunized mice showed a mixed TH1/TH2 immune response (IgG1/IgG2 ratio of 1). No increase T-cell proliferation was observed in the DNA-immunized mice.

This study shows, in a wild-type mouse model, DNA Abeta42 trimer immunization protocol produced a TH2 immune response and appeared to have low potential to cause an inflammatory T-cell response.

Lambracht-Washington D et al. Arch Neurol. 2009; 302(16):1796-802.

HORMONE THERAPY, COGNITIVE FUNCTION, AND DEMENTIA

Postmenopausal hormone therapy (HT) remains the most effective treatment for alleviating menopausal symptoms, which affect up to 80% of women, yet its effect on cognitive aging remains controversial.

A research group from the University Montpellier, Montpellier, France, conducted a prospective study to examine the association between HT and cognitive performance or dementia, focusing on the duration and type of treatment used, as well as the timing of initiation of HT in relation to the menopause.

Women 65 years and older were recruited in France as a part of the Three City Study. At baseline and 2- and 4-year follow up, women were administered a short cognitive test battery and a clinical diagnosis of dementia was made. Detailed information on current and past HT use was also gathered. The types of HT included estrogen alone, oral estrogen and progestogen, and transdermal estrogen and progestogen (natural progesterone and synthetic progestin). Analysis was adjusted for a number of socio-demographic, behavioral, physical, and mental health variables, as well as apolipoprotein E (ApoE) genotype.

Among 3,130 naturally postmenopausal women, current HT users performed significantly better than never users on verbal fluency, working memory, and psychomotor speed. These associations varied according to the type of treatment and a longer duration of HT appeared to be more beneficial. However, initiation of HT close to the menopause was not associated with better cognition. HT did not significantly reduce dementia risk over 4 years but current treatment diminished the negative effect associated with ApoE E4.

Results showed that current HT was associated with better performance in certain cognitive domains but these associations were dependent on the duration and type of treatment used. It also showed that there is no evidence that HT needs to be initiated close to the onset of menopause to have a beneficial effect on cognitive function in later life. Current HT may decrease the risk of dementia associated with the ApoE E4 allele.

Ryan J et al. *Neurology*. 2009; 73(24):1729-37.

PHYSICAL ACTIVITY AND RISK OF ISCHEMIC STROKE

The Northern Manhattan Study is a prospective cohort (n=3,298) study in older, urban-dwelling, multiethnic, stroke-free individuals. Baseline measures of leisure-time physical activity were collected via in-person questionnaires. Cox proportional hazards models were constructed to examine whether energy expended and intensity of physical activity were associated with the risk of incident ischemic stroke.

Physical inactivity was present in 40.5% of the cohort. Over a median follow-up of 9.1 years, there were 238 incident ischemic strokes. Moderate- to heavy-intensity physical activity was associated with a lower risk of ischemic stroke. Engaging in any physical activity vs. none and energy expended in kcal/wk were not associated with ischemic stroke risk. There was an interaction of gender with intensity of physical activity, such that moderate to heavy activity was protective against ischemic stroke in men, but not in women.

Results suggest that moderate- to heavy-intensity physical activity, but not energy expended, is protective against risk of ischemic stroke independent of other stroke risk factors in men in the study cohort. Engaging in moderate to heavy physical activities may be an important component of primary prevention strategies aimed at reducing stroke risk.

Willey JZ et al. *Neurology*. 2009; 73(24):1774-79.

AMYLOID DYNAMICS ARE REGULATED BY OREXIN AND THE SLEEP-WAKE CYCLE

There are many factors regulating amyloid beta accumulation, and their mechanisms are only partly understood.

Abeta aggregation is a concentration-dependent process that is likely responsive to changes in brain interstitial fluid (ISF) levels of Abeta. Using in vivo microdialysis in mice, researchers from Washington University found that the amount of ISF Abeta correlated with wakefulness. The amount of ISF Abeta also significantly increased during acute sleep deprivation and during orexin infusion, but decreased with infusion of a dual orexin receptor antagonist. Orexin is a molecule that regulates wakefulness and other physiological functions, and is strongly implicated in narcolepsy and cataplexy, as well as disorders of sleep and arousal. Chronic sleep restriction significantly increased, and a dual orexin receptor antagonist decreased, Abeta plaque formation in amyloid precursor protein transgenic mice.

This result suggests that the sleep-wake cycle and orexin may play a role in the pathogenesis of Alzheimer's disease.

Kang J-E et al. Science. 2009; 326:1005-7.

PITTSBURGH COMPOUND B IMAGING AND PREDICTION OF PROGRESSION FROM COGNITIVELY NORMAL TO DEMENTIA DUE TO ALZHEIMER'S DISEASE

A research group lead by Dr. John Morris from the Alzheimer's Research Center, Washington University, St. Louis, conducted a longitudinal cohort study to determine whether preclinical Alzheimer's disease (AD), as detected by the amyloid-imaging agent Pittsburgh Compound B (PiB) in cognitively normal older adults, is associated with risk of symptomatic AD.

A total of 159 cognitively normal participants with a mean age of 71.5 years with a Clinical Dementia Rating (CDR) of 0 were assessed with PET to determine the mean cortical binding potential for PiB and followed up with annual clinical and cognitive assessments for progression to very mild dementia of the Alzheimer's type (DAT).

Twenty-three participants progressed to CDR 0.5 at follow-up assessment (range: 1-5 assessments after PET PiB). Of these, 9 were diagnosed with DAT. Higher mean cortical binding potential values for PiB and age predicted progression to CDR 0.5 DAT. The CDR 0.5 DAT group showed decline in 3 cognitive domains – episodic memory, semantic memory, and visuospatial performance, and had volume loss in the parahippocampal gyrus (includes entorhinal cortex) compared with individuals who remained at CDR 0.

This study suggests that preclinical AD as detected by PET PiB is not benign, as it is associated with progression to symptomatic AD.

Morris J et al. Arch Neurol. 2009; 66(12):1469-75.

DISTINCT ANATOMICAL SUBTYPES OF THE BEHAVIORAL VARIANT OF FRONTOTEMPORAL DEMENTIA

The behavioral variant of frontotemporal dementia (FTD) is a progressive neurodegenerative syndrome characterized by changes in personality and behavior. It is typically associated with frontal lobe atrophy although the patterns of atrophy are heterogeneous.

Dr. Jennifer L. Whitwell from the Dept. of Radiology, Mayo Clinic, and her colleagues conducted a study to examine case-by-case variability in patterns of grey matter atrophy in FTD patients

with the behavioral variant, and to investigate whether behavioral variant of FTD can be divided into distinct anatomical subtypes.

For 66 patients with the behavioral variant of FTD, grey matter volumes were obtained for 26 regions of interest, including frontal, temporal and parietal lobes, striatum, insula and supplemental motor area, using the automated anatomical labeling atlas. Regional volumes were divided by total grey matter volume, and a hierarchical agglomerative cluster analysis was performed to cluster the behavioral variant of FTD patients into different anatomical clusters.

There were 4 useful clusters identified with distinct patterns of grey matter loss, two of which were associated with temporal lobe volume loss, with one subtype showing loss restricted to temporal lobe regions and the other to temporal as well as frontal and parietal lobes. Another 2 subtypes were characterized by a large amount of frontal lobe volume loss, with one subtype showing grey matter loss in the frontal and temporal lobes and the other relatively restricted to the frontal lobes. These 4 subtypes differed on clinical measures of executive function, episodic memory and confrontation naming. The cluster did not differ in behavioral severity as measured by the Neuropsychiatric Inventory, supporting the original classification of the behavioral variant of FTD in these patients.

This result suggests that behavioral variant of FTD can be subdivided into 4 different anatomical subtypes.

Whitwell JL et al. *Brain*. 2009; 132(11):2932-46.

EFFECT OF MEMANTINE ON CSF BIOMARKERS OF NEUROFIBRILLARY PATHOLOGY

Previous studies showed that memantine inhibits tau hyperphosphorylation *in vitro*. In this study Dr. Lidia Glodzik from New York University School of Medicine and her colleagues measured phosphorylated tau (P-tau) and total tau (T-tau) before and after 6 month treatment with memantine in 12 subjects ranging from normal cognition with subjective memory complaints, through mild cognitive impairment to mild Alzheimer's disease. Thirteen non-treated individuals served as controls.

Results show that the treatment was associated with a reduction of P-tau in subjects with normal cognition. No treatment effects were seen among impaired individuals, suggesting that longer treatment time may be needed to achieve a biomarker effect in this group.

Glodzik et al. *JAD*. 2009; 18(3):509-13.

STATIN TREATMENT AND STROKE OUTCOME IN THE SPARCL TRIAL

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial is a placebo-controlled, randomized trial designed to determine whether treatment with atorvastatin reduces strokes in subjects with recent stroke or transient ischemic attack (n=4,731).

Using the SPARCL data, Dr. Larry B. Goldstein from the Division of Neurology, Duke University, and his colleagues investigated whether treatment favorably shifts the distribution of severities of ischemic cerebrovascular outcomes.

Stroke severity was assessed with the NIH Stroke Scale, Barthel Index, and modified Rankin Scale score (mRS) at enrollment (1 to 6 months after the index event) and 90 days post-stroke in subjects having a stroke during the trial.

Over 4.9 years, strokes occurred in 576 subjects. There was reduction in fatal, severe (mRS: 5 or 4), moderate (mRS: 3 or 2), and mild (mRS: 1 or 0) outcome ischemic strokes, and transient ischemic attacks, and an increase in the proportion of event-free subjects randomized to atorvastatin. Results were similar for all outcome events with no effect on outcome hemorrhagic stroke severity. When the analysis is restricted to those having an outcome ischemic stroke, there was only a trend toward lesser severity with treatment based on the mRS with no difference based on the NIH Stroke Scale of Barthel Index.

This study suggests that the outcome of recurrent ischemic cerebrovascular events might be improved in statin users as compared with nonusers.

Goldstein LB et al. Stroke. 2009; 40:3526-31.

THE EXISTENCE OF COGNITIVE PLATEAUS IN ALZHEIMER'S DISEASE

Dr. Andrea C. Bozoki from the Department of Neurology, Michigan State University and her colleagues evaluated the existence of cognitive plateaus in some individuals during the course of Alzheimer's disease (AD).

Data came from the historical patient group collected via The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (1988-1996). Data reduction was performed by using principal component analysis to derive a single cognitive measure (F1), followed by application of a novel plateau-searching algorithm to individual patient data, looking for stable period of 3 year or longer. To evaluate the time dependence of F1, a linear mixed model was fitted to the group and to individual data points.

Twenty-two percent of AD subjects (54/423) and 98% of healthy control subjects (253/258) exhibited a plateau. Within the AD plateau group, the most common pattern was a single plateau (mean: 3.6 years; range: 3 to 7 years) that extended for the entire measurement period (28/54 subjects). Briefer plateau durations were seen at the beginning or end of the measurement period. Initial cognitive function (F1) was slightly higher in the plateau group, which was also slightly older and less well-educated.

In a patient sample predating the widespread use of cholinesterase inhibitors, about 20% with AD demonstrated periods of prolonged cognitive stability. This significant inter-individual variability should be considered when providing prognostic information to families and when assessing individual patient responses to pharmacotherapy. This study suggests a caution when assessing results of potentially disease-modifying agents at the individual patient level.

Bozoki AC et al. Alz & Dem. 2009; 5(6):470-8.

CHOLINESTERASE INHIBITORS AND INCIDENCE OF BRADYCARDIA IN PATIENTS WITH DEMENTIA

A research group from the VA Boston Healthcare System conducted a study to quantify the association between cholinesterase inhibitors (ChE-Is) and a new diagnosis of bradycardia and to evaluate the clinical significance of bradycardia.

In patients with dementia who received care between January 1999 and June 2007 (N=11,328) in the New England VA Healthcare System, bradycardia was defined by 3 methods using a combination of ICD-9 codes and recorded heart rates of less than 60 beats per minutes. Cox proportional hazards with time-dependent exposures were used to evaluate the association and

to examine the dose effect for donepezil and bradycardia.

A greater risk for bradycardia was found in patients taking any ChE-Is than in the no-treatment group. A dose-response effect was observed for donepezil, with the highest-dose group at greatest risk. Patients with bradycardia were more likely to fall, experience syncope, or need a pacemaker implantation than those without.

Using a large cohort, this study showed a modestly greater risk for bradycardia in patients with dementia taking ChE-Is than in those not taking these drugs. In patients taking donepezil, the risk of bradycardia may increase with increasing dose. Due to the potential clinical consequences, monitoring for bradycardia may be warranted in patients with dementia treated with ChE-Is.

Hernandez RK et al. JAGS. 2009; 57(11):1997-2003.

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