

Memory Care Monthly

Supporting Healthcare Professionals in Caring for the Aging

March / April 2009

PREVENTING ALZHEIMER'S BY 2020

In the March 2009 issue of Alzheimer's & Dementia, the journal of National Alzheimer's Association, thought leaders contributed to lay a clear roadmap for preventing Alzheimer's disease by the year 2020. The vision and recommendation featured in the journal is based on 3 think-tank meetings held in 2007 and 2008, and represents collective thoughts from over 70 leaders worldwide in the areas of Alzheimer's disease and dementia.

Alzheimer's & Dementia, the journal of Alzheimer's Association, Vol.5, No.2, 2009.

Link: <http://www.alzheimersanddementia.org>

WHAT'S NEW?

FOR MORE TIMELY NEWS, VISIT OUR "BRAIN TODAY" BLOG

Myriad news reports about brain health are published every day. The news covers many related topics such as memory loss, Alzheimer's disease, drugs and treatments, risk factors, diagnostic tests, and published discoveries across the field. Some of the news is objectively reported, some is over-sensationalized, and some is intentionally misleading. This blog is devoted to interpreting the daily news and distilling its true value.

<http://braintoday.blogspot.com>

FEATURED ARTICLE

DIFFERENT HIPPOCAMPAL REGIONS ASSOCIATED WITH MEMORY LOSS

A research group lead by Dr. Scott A. Small from Columbia University has investigated whether and how late-life diseases such as diabetes and stroke contribute to age-related cognitive decline.

Functional MRI (fMRI) was used to determine brain infarcts and to generate high-resolution functional maps of the hippocampal formation in 240 community-based, non-demented elders (mean age, 79.7 years) who received a comprehensive medical evaluation. Sixty participants had type 2 diabetes mellitus, whereas 74 had MRI-documented brain infarcts, and the first analysis was designed to pinpoint hippocampal sub-regions differentially linked to each disorder. Then, guided by the results, additional fMRI studies in aging rhesus monkeys and mice were

used to test proposed mechanisms of dysfunction.

Researchers found that although both diabetes and brain infarcts were associated with hippocampal dysfunction, each was linked to separate hippocampal sub-regions, suggesting distinct underlying mechanisms. The hippocampal sub-region linked to diabetes implicated blood glucose as a pathogenic mechanism, a hypothesis confirmed by imaging aging rhesus monkeys and a mouse model of diabetes. The hippocampal sub-region linked to infarcts suggested transient hypoperfusion as a pathogenic mechanism, a hypothesis provisionally confirmed by comparing anatomical patterns across subjects with infarcts in different vascular territories.

These results show how diseases of late life differentially target the hippocampal formation, identify elevations in blood glucose as a contributing cause of age-related memory decline, and suggest high importance of intervening against late-life diseases to preserve cognitive health.

Wu W et al. *Annals of Neurology*. 2008; 64(6):698-706.

RESEARCH UPDATES

TREATMENT PRACTICE OF MILD COGNITIVE IMPAIRMENT IN CALIFORNIA ALZHEIMER'S DISEASE CENTERS

“Real world” treatments for patients with mild cognitive impairment (MCI) were examined at the California Department of Public Health, Alzheimer’s Disease Research Centers of California. This study was lead by Dr. Kristine Yaffe from UC San Francisco and VA Medical Center San Francisco.

Of 578 patients with MCI, 166 patients (28.7%) were taking anti-Alzheimer’s medications, and this treatment was associated with greater functional impairment, higher education, certain MCI subtypes and older age. 252 patients (43.6%) were taking statins, and the use was associated with diabetes mellitus, hypertension, myocardial infarct, male gender, and MCI subtype. 115 patients (19.9%) were taking anti-oxidants, and the use were associated with higher education and diabetes mellitus and varied according to site. 37 patients (6.4%) were taking folic acid, and the use were associated with nonwhite race, male gender, and greater functional impairment.

This study also suggested that the patients with MCI are frequently being treated “off label” with cholinesterase inhibitors, memantine, and/or other cognition enhancing drugs.

Weinstein A et al. *JAGS*. 2009; 57(4):686-90.

CEREBRAL INFARCT AND COGNITIVE PERFORMANCE

Although cerebral infarcts increase the risk for cognitive impairment, the relation between location and number of infarcts and cognitive function is not well studied.

Dr. Jane S. Saczynski from the University of Massachusetts Medical School and her colleagues studied the cross-sectional association between number and location of infarcts and cognitive performance and found that having infarcts in >1 location is associated with poor performance in memory, processing speed, and executive function, independent of cardiovascular co-morbidities, white matter lesions, and brain atrophy. This suggests that both the number and the distribution

of infarcts jointly contribute to cognitive impairment.

From the Age Gene/Environments Susceptibility-Reykjavik Study data, 4030 non-demented participants' composite scores for memory, processing speed, and executive functions were created from a neuropsychological battery, and subcortical, cortical and cerebellar infarcts were identified on brain MRI.

Researchers found that, compared to subjects without infarcts, those with infarcts in multiple locations (n=287 [7%]) had slower processing speed and poorer memory and executive function. Compared to the no infarct group, the presence of either subcortical (n=275) or cortical (n=215) infarcts only was associated with poorer memory performance; a combination of cortical and subcortical infarcts (n=45) was associated with slower processing speed and poorer executive function, while a combination of cerebellar and subcortical infarcts (n=89) was associated with slower processing speed; infarcts in all 3 locations was associated with slower processing speed.

Saczynski JS et al. Stroke. 2009; 40:677-82.

BRAIN VOLUME AND RESISTANCE TO ALZHEIMER'S PATHOLOGIC BURDEN

Autopsy series have shown that some elderly people remain cognitively normal during their lifetime despite a high burden of pathologic lesions associated with Alzheimer's disease (AD) at death. Understanding such resistant mechanisms to AD pathology burden would provide some insights to neuro-protective mechanisms.

A research group led by Dr. Deniz Erten-Lyons from Layton Aging and the Alzheimer's Disease Center, Portland, studied 36 autopsied patients who had Braak stage V or VI and moderate or frequent neuritic plaque scores based on CERAD standards. Of those, 12 had normal cognitive function and 24 a diagnosis of AD before death. Using multiple regression analyses, they found that antemortem hippocampal and total brain volumes were significantly larger in the normal cognition group after adjusting for factors such as demographics, disease stage, and vascular diseases.

The result suggests that large brain and hippocampal volumes might be an important factor for resistance to AD pathologic burden.

Erten-Lyons D et al. Neurology. 2009; 72(4):354-60.

UNCONTROLLED DIABETES INCREASES THE RISK OF ALZHEIMER'S

Researchers from the Karolinska Institute, Stockholm, Sweden, have investigated the association of diabetes with different dementing disorders taking into account glycaemic control, and the link between glucose dysregulation and neurodegeneration. They found that uncontrolled diabetes increases the risk for both Alzheimer's (AD) and vascular dementia (VaD).

A dementia-free cohort (n=1,248) aged ≥ 75 years was longitudinally examined to detect dementia due to AD and VaD cases. The AD diagnoses were further classified into AD with stroke and AD without hypertension, heart disease and stroke. Diabetes was ascertained based on medical history, hypoglycaemic medication use, or a random blood glucose level ≥ 11.0 mmol/l while borderline diabetes was defined as a random blood glucose level of 7.8-11.0. Cox models were used to estimate the hazard (risk) ratios (HRs).

During the 9 year follow-up, 420 individuals developed dementia including 47 VaD and 320 AD.

Of AD cases, 78 had previous, temporally unrelated stroke, and 137 had no major vascular comorbidities. Overall diabetes was only related to VaD (HR 3.21). Undiagnosed diabetes lead to an HR of 3.29. Diabetic patients with <7.5 mmol/l had no increased dementia risk. Uncontrolled and borderline diabetes were further associated with AD without vascular comorbidities.

Xu WL et al. Diabetologia. 2009; March [Epub Ahead of Print].

VASCULAR RISK FACTORS ACCELERATE THE PROGRESSION OF ALZHEIMER'S

Vascular risk factors include medical history (heart disease, stroke, diabetes and hypertension), smoking, and pre-diagnosis blood lipid measures (cholesterol: total, high-density lipoprotein, low-density lipoprotein [LDL-C], and triglyceride concentrations), and these factors may predict how Alzheimer's disease (AD) will progress.

A cohort of 156 patients with AD (mean age at diagnosis: 83 years) was followed for a mean of 3.5 (up to 10.2) years. Cognitive assessments included the domains of memory, abstract reasoning, visual-spatial orientation, language, and executive speed.

Researchers found that higher total cholesterol and LDL-C concentrations and history of diabetes were all associated with faster cognitive decline while high-density lipoprotein cholesterol and triglyceride concentrations were not associated with the rate of decline. Each 10-U increase in cholesterol and KDK-C was associated with a 0.10 standard deviation (SD) decrease in cognitive score per year of follow-up. A history of diabetes was associated with an additional 0.05-SD decrease in cognitive score per year. History of heart disease and stroke were associated with cognitive decline only in the apolipoprotein E4 gene carriers. They also found that only higher LDL-C was independently associated with faster cognitive decline.

Helzner EP et al. JAMA. 2009; 66(3):343-8.

CELLULAR PRION PROTEIN MEDIATES IMPAIRMENT OF SYNAPTIC PLASTICITY BY AMYLOID-BETA OLIGOMERS

Dr. Juha Laurén and his co-investigators from Yale University, New Haven, Connecticut found that cellular prion protein (PrPC) functions as a receptor for the amyloid-beta-42 (Abeta42) oligomers that are known to impair the memory-related functions of synaptic junctions between neurons, especially those in the hippocampus in subjects with Alzheimer's disease (AD). They also found that PrPC's role in mediating the harmful effects of Abeta42 oligomers was not dependent on the infectious, pathogenic conformation of the protein, PrP^{Sc}, which causes fatal transmissible spongiform encephalopathies such as Creutzfeldt-Jakob disease and mad cow disease.

In an analysis of cells that expressed complementary DNA from adult mouse brains, the researchers found that synthetic oligomers of Abeta42 bound only to proteins that were identified as mouse PrP. Abeta42 bound to cells that expressed PrPC with the same apparent affinity as to hippocampal neurons. In more specific analyses of other proteins, they detected several other proteins that bound to oligometric Abeta42, but none of these had the same high affinity and high selectivity for the oligometric peptide as did PrP. However, in cultures of cells from mice that lacked the PrP gene, the researchers found that the binding of Abeta42 to neurons was reduced by only 50%, which indicates that PrPC cannot be the only cell-surface molecule binding Abeta oligomers.

Abeta42 oligomers did not inhibit long-term potentiation (LTP) in hippocampal slices from mice that lacked the PrP gene. LTP in these mice was indistinguishable from baseline levels in wild-type mice. The lack of LTP sensitivity to Abeta42 oligomers in mice without the PrP gene indicates that PrPC acts as a receptor for Abeta42 oligomers mediating inhibition on LTP in wild-type slices or that chronic loss of PrPC may lead to developmental and/or compensatory effects that account indirectly for Abeta42 oligomer ineffectiveness.

This study suggests that PrPC-specific pharmaceuticals may have therapeutic potential for Alzheimer's disease although the interaction between PrPC and Abeta oligomers as well as the relationship between PrPC and patients' cognitive levels must be confirmed in AD patients.

Laurén J et al. *Nature*. 2009; 457:1128-32.

APOE GENOTYPE MODULATES THE EFFECT OF SERUM CALCIUM LEVELS ON COGNITIVE FUNCTION IN OLD AGE

The apolipoprotein (ApoE) genotype and serum calcium levels have been shown to be associated with cognitive impairment. Animal studies have shown variation in ApoE isoforms to play a critical role in intra-neuronal calcium homeostasis, but the contribution of this interaction of cognitive function in human is not known. A research group leads by Dr. P. van Vliet from Leiden University Medical Center, Dept of Gerontology and Geriatrics, Leiden, the Netherlands, studied whether ApoE genotype modulates the association between serum calcium levels and cognitive abilities.

A prospective population-based study of 599 subjects aged 85 years was conducted. Researchers analyzed serum calcium levels and ApoE genotype baseline. During 5-year follow up, cognitive function was annually assessed using the Mini-Mental State Exam (MMSE) and a standardized neuropsychological battery including the 40-item Stroop Test, the Letter Digit Coding Test, and 12 Picture Learning Test.

Both at baseline and during follow-up, high serum calcium levels were associated with worse cognitive function in E3/E4 carriers and to a lesser extent in E3/E3 carriers, but not in E2/E3 carriers. The MMSE score during the entire follow-up period differed between those with high and low serum calcium levels, with 5.5 points in E3/E4 carriers, 1.6 points in E3/E3 carriers, and 0.1 points in E2/E3 carriers.

In summary, ApoE genotype seems to modulate the association between serum calcium levels and cognitive function. High serum calcium levels associated with worse cognitive function, especially in ApoE4 allele carries, but not in carriers of the E2 allele.

van Vliet P et al. *Neurology*. 2009; 72(9):821-8.

CSF BIOMARKERS AND COGNITIVE PROFILES IN ALZHEIMER'S

Researchers have investigated the relationship between CSF biomarkers and cognitive profiles in Alzheimer's disease (AD).

A sample of 177 patients with AD were assessed with the Digit Span, Visual Association Test (VAT), VAT object naming, Trail Making Test (TMT), and category fluency. Disease severity was assessed with the Mini Mental State Exam (MMSE), and functional impairment was rated on the Clinical Dementia Rating Scale. In CSF, levels of amyloid-beta 1-42 (Abeta42), tau, and tau phosphorylated at threonine 181 (p-tau) were measured, and divided into 3 clusters using

K-means cluster analysis – cluster 1 (n=88 [49%]): relatively high levels of Abeta42 and low levels of tau and p-tau; cluster 2 (n=72 [41%]): relatively low levels of Abeta42 and high levels of tau and p-tau; cluster 3 (n=17 [17%]): low levels of Abeta42 and very high levels of tau and p-tau. There were no differences among 3 clusters on demographics, apolipoprotein genotype, disease duration, functional and disease severity. Patients in cluster 3 performed worse on VAT, TMT-A and –B, and fluency, which cannot be explained simply by disease severity.

van der Vlies AE et al. Neurology. 2009; 72(12):1056-61.

A CONTROLLED TRIAL OF ANTIDEPRESSANTS IN PATIENTS WITH PARKINSON'S DISEASE AND DEPRESSION

Depression affects up to 50% of patients with Parkinson's disease (PD), and is associated with a variety of poor outcomes for patients and their families.

Dr. Matthew Menza and his colleagues from the Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey conducted an NIH-funded, randomized, controlled trial of paroxetine CT, nortriptyline, and placebo in 52 patients with PD and depression. The primary outcomes were the change in the Hamilton Depression Rating Scale (HAM-D) and the percentage of depression responders at 8 weeks.

Researchers found that nortriptyline was superior to placebo for the change in HAM-D; paroxetine CR was not. There was a trend for superiority of nortriptyline over paroxetine CT at 8 weeks. Response rates were nortriptyline 53%, paroxetine CR 11%, placebo 24%.

Menza M et al. Neurology. 2009; 72(10):886-92.

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