

Memory Care Monthly

Supporting Healthcare Professionals in Caring for the Aging

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LONG PRODOMAL PHASE OF ALZHEIMER'S DISEASE

Although it is known that cognitive deficits can be detected long before the typical symptoms of Alzheimer's disease (AD) become evident, the onset of cognitive decline has not been well studied. However, the new study lead by Dr. Helene Amieva showed the 14-year course preceding dementia stage with orderly pattern of cognitive deficits, providing opportunities for early detection and intervention of AD.

Dr. Amieva and her colleagues from Institut National de la Sante et de la Recherche Médicale in France utilized the Personnes Agées Quid (PAQUID) longitudinal study to examine the emergence of the first clinical symptoms over a 14-year period of follow-up before the dementia phase of AD.

Of the 3,777 initial subjects of the PAQUID cohort, 350 subjects developed AD during the 14 years of follow-up. The cases were matched to 350 elderly controls. The cognitive functions, activities of daily livings (ADLs), and depression scores were assessed throughout the 14-year follow-up using a semi-parametric extension of the mixed-effects linear model.

The first decline in cognitive performances appeared as early as 12 years before the dementia phase in measures of semantic memory and conceptual formation followed by global deficits associated with increased complaints and depressive symptoms. About 2 years later, as a consequence of cognitive dysfunction, the subjects started to become slightly dependent in their ADLs. In the last 3 years, the impairment significantly worsened until the subjects reached the dementia phase.

This study provides a clear illustration of the particularly long and progressive prodromal phase of AD, and shows the successive emergence of cognitive deficits, depressive symptoms, and functional impairment during this phase.

Amieva H. et al. Ann Neurol. 2008; 64(5):492-8.

FEATURED ARTICLE

ADHERING TO STROKE GUIDELINE IS ASSOCIATED WITH SUSTAINED IMPROVEMENT IN CARE FOR STROKE PATIENTS

"Get with the Guideline – Stroke" is a guideline made available in 2003 by the American Heart Association to bridge gap in stroke treatment. It offers the latest evidence-based treatments and training to help medical staff provide consistent and quality care for stroke patients.

Dr. Lee H. Schwamm and his colleagues investigated whether participation in Get With the Guidelines-Stroke was associated with improvements in adherence. They measured adherence to guideline recommendations in 322,847 hospitalized patients discharged with a diagnosis of ischemic stroke or transient ischemic attack. A volunteer sample of 790 US academic and community hospitals participated from 2003 through 2007. The main outcome measures were change in adherence over time to 7 pre-specified performance measures and a composite measure.

Researchers found that participation in Get With the Guidelines-Stroke was associated with improvements in the 7 individual and 1 composite measures from baseline to the fifth year: intravenous thrombolytics (42.09% vs. 72.84%), early antithrombotics (91.46% vs. 97.04%), deep vein thrombosis prophylaxis (73.79% vs. 89.54%), discharge antithrombotics (95.68% vs. 98.88%), anticoagulation for atrial fibrillation (95.03% vs. 98.39%), lipid treatment for low-density lipoprotein >100 mg/dL (73.63% vs. 88.29%), smoking cessation (65.21% vs. 93.61%), and composite (83.52% vs. 93.97%).

The results show that participating to Get With the Guidelines-Stroke program was associated with increased adherence to all stroke performance measures, and improved stroke care in all participated hospitals regardless of size, geography, and teaching status.

Schwamm LH et al. *Circulation*. 2009; 119(1):107-15.

RESEARCH UPDATES

VALPROIC ACID INHIBITS ABETA PRODUCTION, NEURITIC PLAQUE FORMATION, AND BEHAVIORAL DEFICITS IN ALZHEIMER'S MOUSE MODELS

Dr. H. Qing and his colleagues from University of British Columbia, Vancouver, Canada, reported that valproic acid (VPA) inhibits the production of beta amyloid (Abeta) and neurotic plaque formation in transgenic Alzheimer's disease (AD) model mice.

VPA is one of the most widely used anticonvulsant and mood-stabilizing agents for treating epilepsy and bipolar disorder. The researchers found that VPA decreased Abeta production by inhibiting GSK-3beta-mediated gamma-secretase cleavage of APP both in vitro and in vivo. VPA treatment significantly reduced neuritic plaque formation and improved memory deficits in transgenic AD model mice. They also found that early application of VPA was important for reducing memory deficits of AD model mice. This study suggests that VPA may be beneficial in the prevention and treatment of AD.

Qing H et al. *J Exp Med*. 2008; 205(12):2781-9.

PREVALENCE AND CORRELATES OF SILENT CEREBRAL INFARCTS - THE FRAMINGHAM OFFSPRING STUDY

The prevalence of silent cerebral infarction (SCI) on MRI in community-based samples has been previously estimated at between 5.8% and 17.7% depending on age, ethnicity, presence of comorbidities, and imaging techniques. In this study, Dr. Rohit R. Das and his colleagues from Department of Neurology, Boston University, analyzed the prevalence and risk factors

associated with SCI at midlife in the community-based Framingham sample.

The study sample comprised 2,040 Framingham Offspring (53% female; mean age, 62+/-9 years) who attended the sixth examination (1996-1998), underwent volumetric brain MRI (1999-2005,) and were free of clinical stroke at MRI. The researchers examined the age- and gender-specific prevalences and the clinical correlates of SCI using multivariable logistic regression models.

The study found that at least 1 SCI was present in 10.7% of participants; 84% had a single lesion. SCI was largely located in the basal ganglia (52%), other subcortical (35%) areas, and cortical areas (11%). Prevalent SCI was associated with the Framingham Stroke Risk Profile score (OR, 1.27; 95% CI, 1.10-1.46); stage I hypertension determined by JNC-7 criteria (OR, 1.56; CI, 1.15-2.11), an elevated plasma homocysteine in the highest quartile (OR, 2.23; CI, 1.42-3.51), atrial fibrillation (OR, 2.16; CI, 1.07-4.40), carotid stenosis >25% (OR, 1.62; 1.13-2.34), and increased carotid intimal-medial thickness above the lowest quintile (OR, 1.65; CI, 1.22-2.24).

The prevalence and distribution of SCI in the Framingham Offspring were similar to previous estimates. Risk factors previously associated with clinical stroke were also found to be associated with midlife SCI. These results support current guidelines emphasizing proactive detection and treatment of stroke risk factors.

Das RR et al. Stroke. 2008; 39(11):2929-35.

ALZHEIMER'S DISEASE AND COGNITIVE RESERVE: VARIATION OF EDUCATION EFFECT

Researchers from Alzheimer's Disease Research Center (ADRC), Washington University School of Medicine, St Louis, evaluated the cognitive reserve hypothesis by examining whether individuals of greater educational attainment have better cognitive function than individuals with less education in the presence of elevated fibrillar brain amyloid levels. This study was led by Dr. Catherine M. Roe.

Uptake of carbon 11-labeled Pittsburgh Compound B (^{11}C PiB) was measured for 198 participants (Non-demented=161; dementia of AD type=37) assessed between August 15, 2003, and January 8, 2008, at the Washington University ADRC. Multiple regression was used to determine whether ^{11}C PiB uptake interacted with level of educational attainment to predict cognitive function measured by scores on the Clinical Dementia Rating sum of boxes, Mini-Mental State Examination, and Short Blessed Test and individual measures from a psychometric battery.

The results show that uptake of ^{11}C PiB interacted with years of education in predicting scores on the Clinical Dementia Rating sum of boxes ($P = .003$), the Mini-Mental State Examination ($P < .001$), the Short Blessed Test ($P = .03$), and a measure of verbal abstract reasoning and conceptualization ($P = .02$) such that performance on these measures increased with increasing education for participants with elevated PiB uptake. Education was unrelated to global cognitive functioning scores among those with lower PiB uptake.

Roe CM et al. Arch Neurol. 2008; 65(11):1467-71.

BILATERAL DEEP BRAIN STIMULATION VS. BEST MEDICAL THERAPY FOR PATIENTS WITH ADVANCED PARKINSON DISEASE

Deep brain stimulation has been used for treatment of advanced Parkinson's disease (PD), although there are few randomized trials comparing this to other treatments, and most studies exclude older patients. Dr. Frances M. Weaver and her colleagues from Hines VA Hospital conducted a randomized, controlled trial to compare 6-month outcomes for patients with PD who received bilateral deep brain stimulation (BDBS) or best medical therapy (BMRx).

A total of 255 patients (BDBS of the subthalamic nucleus=60; BDBS of globus pallidus=61; BMRx=134) with PD (Hoehn and Yahr stage \geq 2 while not taking medications) were enrolled; 25% were aged 70 years or older. The primary outcome was time spent in the "on" state (good motor control with unimpeded motor function) without troubling dyskinesia, using motor diaries. Other outcomes included motor function, quality of life, neurocognitive function, and adverse events.

Patients who received BDBS gained a mean of 4.6 h/d of on time without troubling dyskinesia compared with 0 h/d for patients who received BMRx. Motor function improved significantly ($P < .001$) with deep brain stimulation vs. best medical therapy, such that 71% of the BDBS group and 32% of the BMRx group experienced clinically meaningful motor function improvements (\geq 5 points). Compared with the BMRx group, the BDBS group experienced significant improvements in the summary measure of quality of life and on 7 of 8 PD quality-of-life scores ($P < .001$). Neurocognitive testing revealed small decrements in some areas of information processing for patients receiving BDBS vs. BMRx. At least 1 serious adverse event occurred in 49 BDBS patients and 15 best medical therapy patients ($P < .001$). In this trial of patients with advanced PD, BDBS was more effective than BMRx in improving on time without troubling dyskinesias, motor function, and quality of life at 6 months, but was associated with an increased risk of serious adverse events.

Weaver FM et al. JAMA. 2009; 301(1):104-5.

THYROID FUNCTION ABNORMALITIES AND COGNITIVE IMPAIRMENT IN THE ELDERLY

Dr. Graziano Ceresini and his colleagues from Department of Geriatrics, University of Parma, Italy, investigated the relationship between thyroid dysfunction and cognition in older persons.

The sample included 1,171 male and female subjects aged 23 to 102. Thyroid function was evaluated by measuring plasma concentrations of thyrotropin (TSH), free thyroxine (FT4), and free triiodothyronine (FT3). Cognition was evaluated using the Mini-Mental State Examination (MMSE). Prevalence of overt and subclinical thyroid dysfunction was evaluated in different age groups (<65 vs. ≥ 65). Age trends in TSH, FT4, and FT3 were examined in euthyroid (=normally functioning thyroid) subjects. The cross-sectional association between thyroid dysfunction and MMSE score was evaluated adjusting for confounders.

Researchers found that subclinical hypothyroidism and subclinical hyperthyroidism were more prevalent in older than in younger subjects (subclinical hypothyroidism, 3.5% vs. 0.4%, $P < .03$; subclinical hyperthyroidism, 7.8% vs. 1.9%, $P < .002$). In euthyroid participants, TSH and FT3 declined with age, whereas FT4 increased. Older subjects with subclinical hyperthyroidism had lower MMSE scores than euthyroid subjects (22.61 ± 6.88 vs. 24.72 ± 4.52 , $P < .03$). In adjusted analyses, participants with subclinical hyperthyroidism were significantly more likely to have

cognitive dysfunction (hazard rate=2.26, P=.003).

This study showed that subtle age-related changes in FT3, FT4, and TSH occur in individuals who remain euthyroid. Subclinical hyperthyroidism was the most prevalent thyroid dysfunction in older persons and was associated with cognitive impairment.

Ceresini G et al. JAGS. 2009; 57(1):89-93.

REPORTING DEMENTIA ON THE DEATH CERTIFICATES OF NURSING HOME RESIDENTS

Alzheimer's disease (AD) was ranked as the 5th leading cause of death among US residents over 65 years by the National Center for Health Statistics (NCHS) in 2004. NCHS data are derived from death certificates. Retrospective studies of patients who died at various stages of dementia suggest this condition is under reported on death certificates.

Dr. Melissa Wachterman from Brigham and Women's Hospital, Boston, and her colleagues prospectively examined a cohort of nursing home residents who had been diagnosed with end-stage dementia to identify which conditions were documented on their death certificates.

Of the 323 participants with advanced dementia, 165 died during the study follow-up. Among all decedents, dementia documentation on their death certificates was none (37%), listed in part 1 line A (15.8%), listed in part 1 lines B-D (35.2%), and listed in part 2 (16.4%). Among the 114 decedents with a premortem diagnosis of AD, documentation of dementia anywhere on their death certificates was none (33.3%), AD (27.2%), "dementia" without further specification (37.7%), and vascular dementia (0.9%). This study clearly indicates that dementia, and specifically AD, was underreported on death certificates. Also it raises a concern about the accuracy of mortality statistics based on these documents.

Wachterman M et al. JAMA. 2008; 300(22):2608-10.

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