

Memory Care Monthly

Supporting Healthcare Professionals in Caring for the Aging

July / August 2009

MEDICAL CARE CORPORATION PRESENTS AT ICAD 2009

The Alzheimer's Association's 2009 International Conference on Alzheimer's Disease (**ICAD**) was held on July 11-16 in Vienna, Austria. Nearly 3,800 international attendees gathered in Vienna to share their latest research outcomes, thoughts and theories in the area of Alzheimer's disease (**AD**).

This year at ICAD, Medical Care Corporation presented its latest scientific work on improving the measurement of cognitive performance. The presentation, entitled "Reducing Noise In The ADAS-Cog Wordlist Task," evaluated factors affecting the sensitivity of the ADAS-cog, especially in measuring treatment effects in early stage AD, compared with those of the MCI Screen (**MCIS**).

The ADAS-Cog was administered to 112 normal aging and 612 amnesic mild cognitive impairment (**MCI**) AD Cooperative Study subjects. The MCIS was administered to 169 normal aging (=FAST stage 1), 107 MCI (=FAST 3), and 159 mild dementia (=FAST 4) patients from a dementia specialty clinic. Then 40 logistic regressions were performed per sample to estimate each word-trial item odds ratio for predicting normal vs. impaired after controlling for total recall score. Separately, correspondence analysis (CA) was performed to 1) minimize sample differences by double standardizing effects due to subjects and word-trial items; and 2) maximize information explained per word-trial item.

The results showed that the variance explained by word-trial item coefficients from the fixed word order method (MCIS) was 3.02 times that of the shuffled word order method (ADAS-Cog). Using CA, the variances explained by the fixed vs. shuffled word order methods were 30.5% and 22.3% respectively, which is a 37% relative increase.

This study further validates the higher sensitivity and superior clinical utility of the MCIS, which explains more information related to temporal encoding and cumulative learning. The shuffled word order method used in the ADAS-Cog and in the CERAD battery may reduce the ability to detect beneficial effects of disease modifying therapies. This supports an argument to modify standard tools to incorporate a fixed order for the word lists.

WHAT'S NEW?

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

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 to distilling its true value.

<http://braintoday.blogspot.com>

FEATURED ARTICLE

LARGE SAMPLE VALIDATION OF MEMORY PERFORMANCE INDEX

The Memory Performance Index (**MPI**) quantifies the pattern of recalled and non-recalled words of the 10 word recall test onto a 0 to 100 scales and distinguishes normal from non-normal patterns with 96-97% accuracy.

Dr. William Shankle and his colleagues from Medical Care Corporation have evaluated the 10 word recall test data from 121,481 (Normal: N=115,150; Cognitively Impaired: N=5,971) independently living individuals, 18-106 years old (group A), and 441 normal to moderately severely demented patients from dementia specialty clinic (group B).

For group A, the MPI and word recall test immediate free recall (IFR), delayed free recall (DFR), and total free recall (TFR) scores (outcome measures) were each regressed against predictors of age, gender, race, education, test administration method (in person or over the phone), and wordlist used. For group B, the word recall tests and Functional Assessment Staging Tests (FAST) were administered, and median MPI scores were tested for significant differences across FAST stages.

Results show that the variance explained by all predictors combined was MPI=55%, IRF=24.9%, DFR=23.4%, and TFR=26.9% for group A. The age effect size on MPI score was large, but it was small on IFR, DFR, and TFR. All the other predictors had negligible (<0.02) to small effect sizes (0.02 to 0.15). For group B, median MPI scores progressively declined across all FAST stages ($P < .0002$).

This study validates that the MPI score explains 2 to 3 times more variance than total scores (traditional word recall test scoring method), which improves ability to detect treatment effects. In addition, MPI scores progressively declines with increasing dementia severity, which also improves ability to monitor disease progression or treatment effects.

Shankle WR et al. *Alz & Dem.* 2009; 5: 295-306.

RESEARCH UPDATES

PHYSICAL ACTIVITY, DIET AND RISK OF ALZHEIMER'S DISEASE

A research group lead by Dr. Nikolaos Scarmeas from Columbia University Medical Center investigated the combined effect of higher adherence to Mediterranean diet and more physical activity on risk for AD.

They studied 1880 community-dwelling elders (age = 77.2±6.6) without dementia living in New York, NY, with both diet and physical activity information available. Standardized neurological and neuropsychological assessments were administered approximately every 1.5 years from 1992 through 2006, then time to incident AD was examined.

The study found that both higher Mediterranean diet adherence and higher physical activity were independently associated with reduced risk for AD. Compared to no physical activity, 38 to 48 % risk reduction was observed in those who reported some to much physical activities depending on the length and the categories of those activities. Similarly, middle to high adherence to Mediterranean diet reduced the risk for AD by 14 to 40 %.

Scarmeas N et al. JAMA. 2009; 302(6):627-37.

MAPPING OF BRAIN ACETYLCHOLINESTERASE ALTERATIONS IN LEWY BODY AND PARKINSON'S DISEASE BY PET

Previous PET studies showed a significant reduction in cortical acetylcholinesterase (AChE) activity in Parkinson's disease (PD), and a more sizeable decrease in cortical AChE activity in PD with dementia (PDD) and dementia due to Lewy Bodies (DLB) than in Alzheimer's disease (AD). It is not well studied, however, when brain cholinergic deficits occur or how they develop in PD. Furthermore, a difference in brain cholinergic deficits between PDD and DLB has not been studied in detail. To answer these questions, researchers from the National Institute of Radiological Sciences in Chiba, Japan, investigated alterations in brain AChE activity in 9 patients with early PD and 9 with advanced PD, 10 with PDD, 11 with DLB, and 26 healthy controls using PET scans with N-[11C]-methyl-4-piperidyl acetate.

The results showed that, among patients with PD, AChE activity was significantly decreased in the cerebral cortex and especially in the medial occipital cortex (12 % reduction compared with the normal mean). Patients with PDD/DLB, however, had even lower AChE activity in the cerebral cortex (27% reduction). There was no significant difference observed between early and advanced PD, or between DLB and PDD in the amount by which regional AChE activity in the brain was reduced.

This study suggests that brain cholinergic dysfunction occurs in the cerebral cortex especially in the medial occipital cortex. It begins in early PD, and then spreads widely and becomes profound in both PDD and DLB.

Shimada H et al. Neurology. 2009; 73(4):273-8.

MRI AND CSF BIOMARKERS IN NORMAL, MCI AND ALZHEIMER'S

Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a research group lead by Dr. Prashanthi Vemuri from the Mayo Clinic and Foundation investigated the correlation of both MRI and CSF biomarkers with clinical diagnoses with cognitive performance in cognitively normal (CN) subjects and patients with amnesic mild cognitive impairment (aMCI), and patients with Alzheimer's disease (AD). They also investigated the predictive power of MRI and CSF biomarkers for future clinical changes.

The data from ADNI consisted of baseline CSF (t-tau, Aβ₁₋₄₂, and p-tau_{181P}) and MRI scans, Structural Abnormality Index (STAND) scores, which reflect the degree of AD-like anatomical features on MRI, cognitive assessments and dementia severity measures from 109 CN subjects,

192 with aMCI and 98 with AD.

The results showed that there was no significant correlation between CSF biomarkers and cognitive scores in any of the study groups individually. However, STAND scores correlated with both Clinical Dementia Rating-sum of boxes and MMSE in the aMCI and AD groups. While STAND and all CSF biomarkers were predictors of clinical group membership (CN, aMCI, or AD) univariately, STAND was more predictive than CSF both univariately and in combined models. This suggests that, although MRI and CSF provide complementary information, MRI reflects clinically defined disease stages better than the CSF biomarkers tested.

In terms of future clinical changes, MRI and CSF also provided complimentary predictive information about time to conversion from aMCI to AD, and combination of the 2 provided better prediction than either source alone. However, MRI was found to be a slightly better predictor of future clinical and functional decline than CSF biomarkers tested.

Vemuri P et al. *Neurology*. 2009; 73(4):287-93.

Vemuri P et al. *Neurology*. 2009; 73(4):294-301.

CSF BIOMARKERS AND INCIPIENT ALZHEIMER'S DISEASE IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT

Dr. Niklas Mattsson and his colleagues from Sahlgrenska University Hospital, Mölndal, Sweden, conducted a large-scale multi-center study to determine the diagnostic accuracy of CSF beta-amyloid 1-42 (Abeta1-42), total tau protein (t-tau), and tau phosphorylated at position threonine 181 (P-tau) for predicting incipient AD in patients with MCI.

The study had 2 parts: a cross-sectional arm involving patients with AD and controls to identify cut-points, followed by a prospective cohort arm involving patients with MCI, conducted from 1990-2007. A total of 750 individuals with MCI, 529 with AD, and 304 controls were recruited by 12 centers in Europe and the United States. Individuals with MCI were followed up for at least 2 years or until symptoms had progressed to clinical dementia.

During follow-up, 271 participants with MCI were diagnosed with AD and 59 with other dementias. The Abeta1-42 assay in particular had considerable inter-site variability, indicating a need for standardization of analytical techniques and clinical procedures. Patients who developed AD had lower median Abeta1-42 and higher P-tau and t-tau levels than MCI patients who did not develop AD during follow-up. The area under the receiver operating characteristic curve was 0.78 for Abeta1-42, 0.76 for P-tau, and 0.79 for t-tau. Cut-offs within sensitivity set to 85% were defined in the AD and control groups and tested in the MCI group, where the combination of Abeta1-42/P-tau ratio and T-tau identified incident AD with a sensitivity of 83%, specificity 72%.

This study showed that CSF biomarkers identify incipient AD with good accuracy. However, these results were less accurate than ones reported from single-center studies.

Mattsson N et al. *JAMA*. 2009; 302(4):385-93.

DISCLOSURE OF APOE GENOTYPE FOR RISK OF ALZHEIMER'S DISEASE

The genotyping of the patients and their family members for apolipoprotein E (ApoE) on the risk of Alzheimer's disease (AD) are not generally recommended partly due to possible psychological distress. However, actual effects have not been well studied.

Dr. Robert C. Green from the Boston University School of Medicine and his colleagues examined the effect of genotype disclosure in a prospective, randomized, controlled trial. They randomly assigned 162 asymptomatic adults who had a parent with AD to receive the results of their own ApoE genotyping (disclosure group) or not to receive such results (nondisclosure group), and measured symptoms of anxiety, depression, and test-related distress 6 weeks, 6 months, and 1 year after disclosure or nondisclosure.

The results showed that no significant short-term psychological risk in both groups, and test-related distress was reduced among those who learned that they were ApoE E4-negative. It also showed that persons with high levels of emotional distress before undergoing genetic testing were more likely to have emotional difficulties after disclosure.

Green RC et al. NEJM. 2009: 361(3);245-54.

RISK AND PREDICTORS OF STROKE IN THE FIRST FEW HOURS AFTER A TIA: POPULATION-BASED STUDY

Several guidelines recommend assessment of patients with TIA within 24 hours. However, it is uncertain how many recurrent strokes occur within 24 hours, and also whether the ABCD2 risk score, the guidelines recommended be use to identify high-risk cases, reliably identifies recurrences in the first few hours.

Dr. Arvind Chandratheva and his colleagues from the Stroke Prevention Research Unit, Oxford University Department of Clinical Neurology, UK, conducted a prospective, population-based incidence study of TIA and stroke with complete follow-up to determine the 6-, 12-, and 24-hour risks of recurrent stroke, defined as new neurologic symptoms of sudden onset after initial recovery.

Of 1,247 first TIA or strokes, 35 had recurrent strokes within 24 hours, all in the same arterial area. The initial event had recovered prior to the recurrent stroke in 25 cases. The 6-, 12-, and 24-hour stroke risks after 488 first TIAs were 1.2%, 2.1% and 5.1%, with 42% of all strokes during the 30 days after a first TIA occurring within the first 24 hours. The 12- and 24-hour risks were strongly related to ABCD2 score.

This study highlights the need for emergency assessment within the first 24 hours of TIA, and also shows the reliability of the ABCD2 scores.

Chandratheva A et al. Neurology. 2009: 72(22);1941-7.

VISUOSPATIAL FUNCTION AS A SIGNIFICANT CONTRIBUTOR TO FUNCTIONAL STATUS IN PATIENTS WITH ALZHEIMER'S DISEASE

Relation of visuospatial abilities to functional status in patients with Alzheimer's disease (AD) has been controversial. Researchers from Showa University Northern Yokohama Hospital investigated whether visuospatial abilities have independent association with functional measures in 57 patients (78.0 +/- 6.1 years) with AD in mild to moderate stages.

They regressed performance on a global cognitive (the revised Hasegawa Dementia Scale: HDSR, total score=30), executive/visuoconstruction (Clock Drawing), visuoperception (Clock Reading: CRT), simple visuoconstruction (figure copying), and frontal behavioral tasks on measures of basic and instrumental activities of daily living (BADL and IADL). Then, independent contributions of these visuospatial measures to functional status were analyzed.

Performance on the CRT contributed significantly to BADL and IADL and the results of HDRS contributed to IADL. Figure copying was related significantly to BADL especially in mild AD.

These results suggest that visuospatial ability is one of the important contributors to functional status.

Fukui T et al. AJADD. 2009: 24(4);313-21.

INTRANASAL DELIVERY OF STEM CELLS

The safety and efficacy of cell-based therapies for neurodegenerative diseases depends on the mode of cell administration. Dr. William H. Frey, II, from the Alzheimer's Research Center at Regions Hospital and the University of Minnesota in St. Paul and his colleagues have found that stem cells delivered intranasally can bypass the blood-brain barrier and make their way into the brain. This method could be useful for delivering other therapies directly into the brain and avoiding the systemic effects that can arise when medicines circulate through the bloodstream.

They hypothesized that intranasally administered cells could bypass the blood-brain barrier by migrating from the nasal mucosa through the cribriform plate along the olfactory neural pathway into the brain and cerebrospinal fluid (CSF). This method would minimize or eliminate the distribution of cellular grafts to peripheral organs and would help to dispense with neurosurgical cell implantation.

They have identified, using transnasal delivery of cells to the brain following intranasal application of fluorescently labeled rat mesenchymal stem cells (MSC) or human glioma cells to naive mice and rats, two migration routes after cells crossed the cribriform plate: (1) migration into the olfactory bulb and to other parts of the brain; (2) entry into the CSF with movement along the surface of the cortex followed by entrance into the brain parenchyma. The delivery of cells was enhanced by hyaluronidase treatment applied intranasally 30 min prior to the application of cells. Intranasal delivery provides a new non-invasive method for cell delivery to the CNS.

Danielyan L et al. Euro J Cell Biol. 2009: 88(6);315-24.

DONEPEZIL DELAYS PROGRESSION TO AD IN MCI PATIENTS WITH DEPRESSIVE SYMPTOMS

Dr. Po H. Lu and his colleagues from the Mary S. E Aston Center for Alzheimer's Disease Research, University of California, Los Angeles, studied 756 patients with amnesic mild cognitive impairment (aMCI) from the 3-year, double-blind, placebo-controlled ADCS drug trial of donepezil and vitamin E to determine whether the presence of depression predicts a higher rate of progression to Alzheimer's disease (AD) and whether donepezil treatment beneficially affects this relationship. The Beck Depression Inventory (BDI) was used to assess depressive symptoms at baseline and patients were followed either to the end of the study or to the primary endpoint of progression to probable or possible AD.

Cox proportional hazards regression, adjusted for age at baseline, gender, apolipoprotein genotype, and the NYU paragraph delayed recall score, showed that higher BDI scores were associated with progression to AD. The sample was stratified into depressed (n = 208) and nondepressed (n = 548) groups. Kaplan-Meier analysis showed that among the depressed group, the proportion progressing to AD was lower for the donepezil group than for the combined vitamin E and placebo groups at 1.7 years, at 2.2 years, and remained marginally lower at 2.7 years.

Within the nondepressed group, the survival curves among the three treatment groups did not differ.

This study suggests that depression is predictive of progression from aMCI to AD, and treatment with donepezil delays progression to AD among depressed patients.

Sadowsky CH et al. AJADD. 2009; 24(3):267-75.

SWITCHING FROM DONEPEZIL TABLETS TO RIVASTIGMINE TRANSDERMAL PATCH IN ALZHEIMER'S DISEASE: THE US 38 STUDY

The US 38 study group lead by Dr. Carl H. Sadowsky investigated safety and tolerability of switching from donepezil to the rivastigmine transdermal patch in patients with mild to moderate Alzheimer's disease (AD).

This prospective, parallel-group, open-label study evaluated immediate or delayed (8 day after discontinuation of donepezil) switch from 5-10 mg/day donepezil to 4.6 mg/24hr rivastigmine following a 4-week treatment period.

Rates of discontinuation due to any reason or adverse events were similar between groups. Incidences of gastrointestinal adverse events were 3.8% in the immediate and 0.8% in the delayed switch group. No patients discontinued secondary to nausea and vomiting. Discontinuation due to application site reactions was low (2.3%). Asymptomatic bradycardia was more common following the immediate switch (2.3% vs. 0%). However, these patients had coexisting cardiac comorbidities.

This study suggests that both immediate and delayed switch strategies were safe and well tolerated, and that the majority of patients may be able to switch directly to rivastigmine transdermal patches without a withdrawal period.

Sadowsky CH et al. AJADD. 2009; 24(3):267-75.

IV IMMUNOGLOBULIN ASSOCIATED WITH A REDUCED RISK OF ALZHEIMER'S DISEASE AND RELATED DISORDERS

A research group lead by Dr. Howard Fillit from the Alzheimer's Drug Discovery Foundation, New York, investigated whether IV immunoglobulin (IVIg) reduced a risk of Alzheimer's disease and related disorders (ADRD).

This retrospective case-control analysis used medical claims for patients over 65 years old from a national database of 20 million age-qualified patients. Cases received 1 or more IVIg administration during April 1, 2001 – August 31, 2004, had claims 1 year prior to first (index) IVIg administration to confirm absence of pre-index ADRD, and had 3 or more years of continuous claims post-index. Untreated controls had their first medical claim during April 1, 2001 – August 31, 2004, and otherwise met the same requirements as cases. Controls were matched 100:1 to cases on age, gender, and risk factors for ADRD including diabetes, hypertension, and obesity. The relative incidence of ADRD post-index for the IVIg-treated cases vs. untreated controls was estimated using Kaplan-Meier survival curve and a Cox proportional hazards model.

The results show that treated patients in the Kaplan-Meier analysis had lower ADRD incidence ($p = 0.02$) with an estimated 2.6% of the 847 IVIg-treated vs. 4.6% of 84,700 controls diagnosed with ADRD at 60 months after index date. It also showed that treated patients in the Cox

proportional hazard model had a 42% lower risk of being diagnosed with ADRD with an estimated 2.8% of treated vs. 4.8% of controls diagnosed with ADRD at 60 months after index date.

Fillit H et al. Neurology. 2009; 73(3):180-5.

PREDICTORS OF MAINTAINING COGNITIVE FUNCTION IN ELDERLY

While several risk factors for cognitive decline have been identified, much less is known about factors that predict maintenance of cognitive function in the elderly.

Dr. Kristine Yaffe and her colleagues from the University of California, San Francisco, studied 2,509 well-functioning black and white elders enrolled in a prospective study. Cognitive function was measured using the Mini-Mental State Exam (MMSE) at baseline and years 3, 5, and 8. Random effects models were used to classify participants as cognitive maintainers (cognitive change slope ≥ 0), minor decliners (slope < 0 and $1 > SD$ below mean), or major decliners (slope $\leq -1 SD$ below mean). Logistic regression was used to identify domain-specific factors associated with being a maintainer vs. a minor decliner.

Over 8 years, 30% of the participants maintained cognitive function, 53% showed minor decline, and 16% had major cognitive decline. Baseline variables significantly associated with being a maintainer vs. a decliner were age, high school education level or greater, ninth grade literacy level or greater, weekly moderate/vigorous exercise, and not smoking.

Some of the factors found in this study are modifiable, and could be implemented in prevention programs to promote successful cognitive aging.

Yaffe K et al. Neurology. 2009; 72(23):2029-35.

Free Patient Brochure

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