Memory Care Monthly

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DIGNIFIED DIAGNOSIS: VOICE FROM THE PATIENTS

In recognition of the changing landscape of Alzheimer's disease, the Alzheimer's Association held four regional town hall meetings with more than 800 participants, including 300 people living with the disease. The outcome of the meetings, summarized as *The 2008 Report: Voices of Alzheimer's Disease*, identified diagnostic challenges and dissatisfying interactions with the medical community as key challenges to address.

Several specific insights were voiced by the meeting participants and published by the Alzheimer's Association as *Principles for a Dignified Diagnosis*. These insights from families and patients with Alzheimer's disease provide suggestions on how to improve the diagnostic challenges and process that both patients and physicians face. These insights include:

- Talk to me (a patient) directly, the person with dementia.
- Tell the truth.
- Test early.
- Take my concerns seriously, regardless of my age.
- Deliver the news in plain but sensitive language.
- Coordinate with other care providers.
- Explain the purpose of different tests and what you hope to learn.
- Give me tools for living with this disease.
- Work with me on a plan for healthy living.
- Recognize that I am an individual and the way I experience this disease is unique.
- Alzheimer's is a journey, not a destination.

As a healthcare professional who touches patient's lives, you might be interested in reading the short document *Principles for a Dignified Diagnosis* (PDF download is also available) at:

http://www.alz.org/news_and_events_dignified_diagnosis_of_dementia.asp

FEATURED ARTICLE

PRIMARY CARE PROVIDERS' VIEWS OF CHALLENGES AND REWARDS OF DEMENTIA CARE RELATIVE TO OTHER CONDITIONS

Despite increasing prevalence and frequency of older patient visits to primary care physician's (PCP's) office, dementia detection in primary care is low, and quality of care for dementia is lower than that for other common conditions. However, as our society rapidly ages, a PCP's role in managing dementia is becoming more critical, yet complex. Although PCPs already manage a broad range of chronic conditions requiring complex care and coordination with specialists,

dementia care calls for further and more frequent care and coordination with caregivers and other family members as well as specialists to address behavioral issues, loss of function, necessary referrals and resources.

Dr. Dorothy P. Harris from the UCLA David Geffen School of Medicine, Dept of Neurology, and her colleagues conducted a cross-sectional survey to compare PCPs' perceptions about dementia and its care within their healthcare organization with perceptions of other common chronic conditions, and to identify factors associated with differences. A total of 230 PCPs from 18 outpatients clinics in 3 San Diego area healthcare organizations participated in the survey. PCPs included internists, family physicians, nurse practitioners, and PAs.

Results show that more PCPs strongly agreed that: older patients with dementia are difficult to manage (23.8%) than for heart disease (5.0%) or diabetes mellitus (6.3%); PCPs can improve quality of life for heart disease (63.8%) and diabetes mellitus (67.6%) than dementia (55.5%); and their organizations have expertise/referral resources to manage diabetes mellitus (49.4%) and heart disease (51.8%) than dementia (21.1%). More PCPs reported almost effortless organizational care coordination for heart disease (13.0%) or diabetes mellitus (13.7%) than for dementia (5.6%), and a great deal or many opportunities for improvement in their ability to manage dementia (50.6%) than incontinence, depression, or hypertension (7.4-34.0%). Internists' views regarding dementia care were less optimistic than those of family physicians, but PCP type was unrelated to views on diabetes or heart disease.

This study has shown that improving primary care management of dementia should directly address PCPs' concerns about expertise and referral resources, difficulty of care provision, and PCP views about prospects for patient improvement.

Harris DP et al. JAGS. 2009; 57(12):2209-16.

RESEARCH UPDATES

ALZHEIMER'S THERAPY COMPLIANCE LINKED WITH LOWER HEALTHCARE COST

A study presented at the 134th Annual Meeting of the American Neurological Association has shown that patients who are initially on oral cholinesterase inhibitors (e.g. rivastigmine, donepezil, galantamine) are compliant during the first year of therapy. Furthermore, they have shown that those who are compliant have lower healthcare costs than those who are noncompliant.

Mrs. Francis Vekeman from Analysis Group, Montreal, Canada, and her colleagues conducted a retrospective claims analysis of 17,717 patients (mean age=81.0; 59.3% female) with Alzheimer's disease (AD) who were newly initiated on an oral cholinesterase inhibitor (ChEI). On average, patient compliance was monitored for 546 days, and was defined as medication procession ratio (MPR): the sum of days' supply of medication divided by the observation period. Persistence was defined as continuous drug use without having a gap of 30 days or more between refills. Healthcare costs associated with compliance and persistence were also observed.

During the first year, the mean MPR was 0.67, and 49.9% were compliant. Kalpan-Meier persistence rates after 6, 12 and 24 months were 52.6, 36.1, and 19.7%, respectively. In the first year of observation, a 15% lower healthcare cost was associated with compliance vs. noncompliance. For inpatient services, the costs for the persistent group totaled $2,372,

compared with a total of $5,025 for the non-persistent group. Total costs for the persistent and non-persistent groups, including pharmacy claims, were $12,592 and $15,421, respectively.

Although there are some limitations to the data, this study has clearly shown that patient's medication compliance goes down within 2 years, which results in higher healthcare costs.

Vekeman et al. the 134th Annual Meeting of the American Neurological Association. 2009.

DIFFERENTIAL ASSOCIATION OF [^{11}C]PIB AND [^{18}F]FDDNP BINDING WITH COGNITIVE IMPAIRMENT

A research group from Department of Neurology and Alzheimer Centre, VU University Medical Centre evaluated associations of [^{11}C]Pittsburgh compound B (PIB) and [^{18}F]FDDNP with impairment in specific cognitive domains over the broader spectrum comprising cognitively normal elderly subjects, patients with mild cognitive impairment (MCI), and patients with Alzheimer's disease (AD).

Paired [^{11}C]PIB and [^{18}F]FDDNP PET scans were performed in 12 patients with AD, 13 with MCI, and 15 cognitively normal elderly subjects. Binding potential (BP_{ND}) was calculated using parametric images of BP_{ND} for global, frontal, parietal, and temporal cortex; medical temporal lobe; and posterior cingulate. Cognitive functions were assessed using a battery of neuropsychological tests. Linear regression was used to assess associations of [^{11}C]PIB and [^{18}F]FDDNP binding with cognitive measures.

Adjusted for age, gender, and [^{18}F]FDDNP binding, higher global [^{11}C]PIB was associated with lower scores on MMSE, immediate and delayed recall of the RAVLT, Visual Association Task, and Trail Making Test part B. In contrast, higher [^{18}F]FDDNP binding was independently associated with lower scores of immediate recall of the RAVLT. After additional adjustment for diagnosis, higher [^{11}C]PIB binding remained independently associated with delayed recall, while [^{18}F]FDDNP remained independently associated with immediate recall. When regional binding was assessed using stepwise models, both increased frontal [^{11}C]PIB and temporal [^{18}F]FDDNP binding were associated with memory, whereas increased parietal [^{11}C]PIB binding was associated with non-memory functions.

In summary, increased [^{18}F]FDDNP binding is specifically associated with impairment of episodic memory, while increased [^{11}C]PIB is associated with impairment in a broader range of cognitive functions.

Tolboom N et al. Neurology. 2009; 73(24):2079-85.

LONGEVITY GENE AND RISK FOR DEMENTIA

As the population ages, there is rising interest in research on longevity and associated genes as well as on the risk for dementia. Some studies have suggested that the apolipoprotein (ApoE) e2 allele is associated with both increased lifespan and lower risk for dementia. Also ApoE e4 has been conclusively associated with increased risk for Alzheimer's disease (AD).

The cholesteryl ester transfer protein (CETP) gene is, like ApoE, involved in central nervous system cholesterol homeostasis and has been associated with exceptional longevity as well as lower cardiovascular risk. However, its association with memory decline and dementia risk is not well understood.

A research group lead by Dr. Richard B. Lipton from the Albert Einstein College of Medicine, tested the hypothesis that a single-nucleotide polymorphism (SNP) at CETP codon 405 (isoleucine to valine V405; SNP rs5882) is associated with a lower rate of memory decline and lower risk of incident dementia including AD.

Data from the Einstein Aging Study for 523 community-dwelling adults without dementia aged 70 years or older with the CETP genotype was analyzed. Standardized neuropsychological and neurological measures were administered annually from 1994-2009. Linear mixed-effects models adjusted for gender, education, race, medical comorbidities, and ApoE e4 examined associations of V405 genotype with longitudinal performance on cognitive tests of episodic memory (Free and Cued Selective Reminding Test [FCSRT]), attention (digit span), and psychomotor speed (digit symbol substitution). The V405 genotype was the main predictor of incident dementia or AD in similarly adjusted Cox proportional hazards models with age as the time scale.

Valine frequency was 43.5%. A total of 40 cases developed incident dementia during follow-up. Results show that, compared with isoleucine homozygotes, valine homozygotes had significantly slower memory decline on the FCSRT(0.43 points decline per year for isoleucine vs. 0.21 for valine). There were no significant differences on the digit span or digit symbol substitution tests. Valine homozygotes also had lower risk of dementia.

This preliminary study suggests that CETP V405 valine homozygosity is associated with slower memory decline and lower incident dementia and AD risk.

Sanders AE et al. JAMA. 2010; 303(2):150-8.

IMPLICATIONS OF SUBJECTIVE COGNITIVE IMPAIRMENT

Subjective cognitive impairment (SCI) in older persons without manifestation of symptoms is a common condition with a largely unclear prognosis. Dr. Barry Reisberg from the Silbertein Aging and Dementia Research Center, New York University School of Medicine, studied whether examining for a sufficient period by using conversion to mild cognitive impairment (MCI) to dementia would clarify SCI prognosis, and whether the prognosis of SCI subjects would differ from that of demographically matched healthy subjects without SCI (no cognitive impairment: NCI).

A consecutive series of healthy subjects, 40 years or older, presenting with NCI or SCI to a brain aging and dementia research center during a 14-year interval, were studied and followed up during an 18-year observation window. The study population (60 NCI, 200 SCI, 60% female) had a mean age of 67.2+/-9.1 years, was well educated (mean 15.5+/-2.7 years), and cognitively normal (MMSE 29.1+/-1.2).

A total of 213 subjects were followed up. Follow-up occurred during a mean period of 6.8+/-3.4 years, and subjects had a mean of 2.9+/-1.6 follow up visits. Seven NCI (14.9%) and 90 SCI (54.2%) subjects declined. Of NCI decliners, 5 declined to MCI, and 2 to probable Alzheimer's disease (AD). Of the 90 SCI decliners, 71 declined to MCI, and 19 to dementia diagnosis. Controlling for baseline demographic variables and follow-up time, SCI subjects had increased decline and declined more rapidly. It also showed that mean time to decline was 3.5 year longer for NCI than for SCI subjects.

These results suggest that SCI in subjects with normal cognition is a possible indication of future decline in most subjects during a 7-year mean follow-up interval. And relevance for community

populations and prevention studies in this at-risk population should be explored.

Reisberg B et al. Alzheimers Dement. 2010; 6(1):11-24.

EFFICACY OF MEDICAL FOOD IN MILD ALZHEIMER'S

Dr. Phillip Scheltens from the Alzheimer Center, VU University Medical Center, Amsterdam, the Netherlands, and his colleagues conducted a randomized, controlled trial to investigate the effect of a medical food on cognitive function in persons with mild Alzheimer's disease (AD).

A total of 225 drug-naïve AD patients were randomized to active product, Souvenaid®, or a control drink, taken once-daily for 12 weeks. Primary outcome measure were the delayed verbal recall task of the Wechsler Memory Scale-revised, and the 13-item modified ADAS-Cog subscale at 12 week.

Results show that significant improvement in the delayed verbal recall task was noted at 12 weeks in the active group compared with the control. Modified ADAS-Cog scores (i.e. cognitive subscale and other outcome scores) were unchanged. This study justifies the further clinical trials of a medical food supplementation in patients with AD.

Scheltens P et al. Alzheimers Dement. 2010; 6(1):1-10.

ABNORMALITIES IN METABOLIC NETWORK ACTIVITY PRECEDE THE ONSET OF MOTOR SYMPTOMS IN PARKINSON'S DISEASE

Imaging studies show that the activity of motor- and cognition-related metabolic brain network is altered in patients with Parkinson's disease (PD). However, it is not known whether the network changes appear at or before symptom onset.

A research group lead by Dr. David Eidelberg from the Feinstein Institute for Medical Research, Manhasset, NY, examined 15 patients with hemiparkinsonian with FDG-PET at baseline, 2.1+/-0.6 and 3.9+/-0.7 years later, and assessed longitudinal changes in network activity in each cerebral hemisphere, focusing specifically on the "pre-symptomatic" hemisphere (ipsilateral to the initially involved body side).

At the network level, the activity of the PD motor- and cognition-related pattern increased symmetrically in both hemispheres over time although significant bilateral elevation were observed at each time point in motor-related pattern while significant elevations were not evident in cognition-related pattern until 4 years. At the regional level, putamen metabolism contralateral to the initially affected body side was elevated at all three time points, without longitudinal change. In contrast, in the initially presymptomatic hemisphere, putamen metabolic acitivity increased steadily over time, reaching abnormal levels only at 4 years. Metabolic activity in the contralateral precuneus fell to subnormal levels by the final time point.

This results suggest that abnormal PD motor-related pattern activity precede the appearance of motor signs by up to 2 years.

Tang CC et al. J. Neurosci. 2010; 30(3):1049-56.

GRID CELLS IN A HUMAN MEMORY NETWORK

Grid cells can be seen in the brains of rats and mice, providing a strikingly periodic

representation of self-location. However, the existence of grid cells in humans and their distributions in the brain are not known.

Dr. Christian F. Doeller and his colleagues from UCL Institute of Cognitive Neuroscience, London, UK, examined, using fMRI, whether particular signals, which are observed in the rats' gird cells in their entorhinal cortex while they are freely moving, can be similarly observed in humans.

When study participants explored a virtual reality environment, mimicking the rats' foraging tasks, fMRI identified the similar signals in a network of enthorhinal/subicular, posterior and medial parietal, lateral temporal and medial prefrontal areas. The effect was strongest in right entorhinal cortex, and the coherence of the directional signal across entorhinal cortex correlated with spatial memory performance.

This study provides evidence for grid-cell-like representation in humans, and implicates a specific type of neural representation in a network of regions that supports spatial cognition and also autobiographical memory.

Doeller CF et al. Nature. 2010; 463:657-61.

COGNITIVE LOSS IN ZINC TRANSPORTER-3 KNOCK-OUT MICE

Zinc trasnporter-3 (ZnT3) protein controls synaptic vesicular Zn^{2+} levels, which is thought to regulate normal cognitive function. In previous studies, 6- to 10-week old ZnT3 knock-out (KO) mice did not show impairment in the Morris water maze. Therefore, Dr. Paul A. Adlard and his colleagues examined whether older ZnT3 KO mice exhibit age-dependent deficits in learning and memory that are manifest at 6 months but not at 3 months of age.

They found that that these deficits were associated with significant alterations in key hippocampal proteins involved in learning and memory, as assessed by Western blot. These included decreased levels of the presynaptic protein SNAP25; the postsynaptic protein PSD95; the glutamate receptors AMPAR, NMDAR2a, an NMDAR2b; the surrogate marker of neurogenesis doublecortin; and elements of the BDNF pathway, pro-BDNF and TrkB. In addition, there was a concomitant decrease in neuronal spine density. They also found that cortical ZnT3 levels fall with age in wild-type mice, in healthy older humans, and particularly in patients with Alzheimer's disease (AD).

This study suggests that age-dependent loss of transsynaptic Zn^{2+} movement leads to cognitive loss, and since extracellular beta-amyloid is aggregated by and traps this pool of Zn^{2+}, the genetic ablation of ZnT3 may represent a phenocopy for the synaptic and memory deficits of AD.

Adlard PA et al. J. Neurosci. 2010; 30(5):1631-6.

GENE THERAPY FOR PARKINSON'S DISEASE

In Parkinson's disease (PD), the benefit of levodopa therapy becomes less marked over time, perhaps because degeneration of nigrostrial neurons causes progressive loss of aromatic l-amino acid decarboxylase (AADC), the enzyme that converts levodopa into dopamine. In a primate model of PD, intrastriatal infusion of an adeno-associated viral type 2 vector containing the human AADC gene (AAV-hAADC) results in robust response to low-dose levodopa without the side effects associated with higher doses.

A research group lead by Dr. Michael J. Aminoff from the UCSF Department of Neurology investigated the effect of a gene therapy in patients with PD. Patients with moderately advanced PD received bilateral intraputaminal infusion of AAV-hAADC vector. Low-dose and high-dose groups (5 patients in each) were studied using standardized clinical rating scales at baseline and 6 months. PET scans using the AADC tracer [18F]fluoro-l-m-tyrosine (FMT) were performed as a measure of gene expression.

Although the gene therapy was generally well tolerated, 1 symptomatic and 2 asymptomatic intracranial hemorrhages followed the operative procedure. Total and motor rating scales improved in both groups. Motor diaries also showed increased on-time and reduced off-time without increased “on” time dyskinesia. At 6 months, FMT PET showed a 30% increase of putaminal uptake in the low-dose cohort and a 75% increase in the high-dose cohort.

This study supports that bilateral intrastriatal infusion of adeno-associated viral type 2 vector containing the human AADC gene improves mean scores on the Unified Parkinson’s Disease Rating Scale by approximately 30% in the on and off states, but the surgical procedure may be associated with an increased risk of intracranial hemorrhage and self-limited headache.

Christine CW et al. Neurology. 2009: 73(20):1662-9.

OVERLAPPING ATROPHY PATTERNS OF AGING AND EARLY ALZHEIMER’S

Dr. Cyrus A. Raji from the University of Pittsburg, School of Medicine, and his colleagues evaluated the independent and overlapping patters of gray matter (GM) atrophy in normal aging and Alzheimer’s disease (AD).

A total of 169 cognitively normal subjects (age=77.6+/-3.6) and 33 persons with probable AD (age=82.8+/-5.2) enrolled in the longitudinal Cardiovascular Health Study-Cognitive Study underwent 3-dimensional volumetric MCI scans. Control subjects remained cognitively normal for at least 5 years after their MRI scans and the probable AD subjects were relatively early in their clinical course (average modified MMSE=76/100).

After adjusting for total intracranial volume, gender, education, and race, with older age, GM volume was lower in the sensorimotor and heteromodal association areas in frontal, temporal, occipital, and parietal lobes, as well as in the cerebellum. Additional atrophy was observed in the posterior hippocampus, thalamus, and middle cingulated gyrus. By contrast, atrophy was seen in subjects with AD in the anterior hippocampal/parahippocampal regions and the precuneus. Normal aging and AD overlapped in the hippocampal body and the entorhinal cortex.

This study has shown that aging and AD exert independent GM atrophy patterns but these effects overlapped substantially in the hippocampus and entorhinal cortex.

Raji CA et al. Neurology. 2010: 73(22);1899-905.

A PHASE 2 MULTIPLE ASCENDING DOSE TRIAL OF BAPINEUZUMAB IN MILD TO MODERATE ALZHEIMER’S DISEASE

Bapineuzumab, an antibody targeted against the N-terminus of Abeta, is a passive Abeta immunotherapy being currently tested for Alzheimer’s disease (AD). Bapineuzumab is hypothesized to bind to Abeta in the brain and facilitate its removal, yielding beneficial clinical effects. In this study, bapineuzumab was evaluated in a multiple ascending dose, safety and efficacy study in mild to moderate Alzheimer’s disease (AD).

The study enrolled 234 patients, randomly assigned to IV bapineuzumab or placebo in 4 dose cohorts (0.15, 0.5, 1.0, or 2.0 mg/kg). Patients received 6 infusions, 13 weeks apart, with final assessments at week 78. The pre-specified primary efficacy analysis in the modified intent-to-treat population assumed linear decline and compared treatment differences within dose cohorts on the ADAS-Cog and Disability Assessment for Dementia. Exploratory analyses combined dose cohorts and did not assume a specific pattern of decline.

Results showed no significant differences in the primary efficacy analysis. Exploratory analyses showed potential treatment differences on cognitive and functional endpoints in study "completers" and ApoE e4 non-carriers. Reversible vasogenic edema, detected on brain MRI (12/124) bapineuzumab-treated patients, was more frequent in higher dose groups and ApoE e4 carriers.

Salloway S. Neurology. 2009; 73(24):2061-70.

ASSOCIATION OF VITAMIN D DEFICIENCY WITH COGNITIVE IMPAIRMENT IN OLDER WOMEN

Dr. Cedric Annweiler from the Dept. of Internal Medicine and Geriatrics, Angers University Hospital, and his colleague conduced a cross-sectional population-based study to examine the association between serum 25(OH)D deficiency and cognitive impairment while taking confounders (e.g. age, BMI, number of chronic diseases, hypertension, depression, medication etc.) into account.

A total of 752 women aged 75 years or older from the Epidémiologie de l'Ostéoporose (EPIDOS) cohort were divided into 2 groups according to serum 25(OH)D concentrations (either deficit: <10 ng/mL, or nondeficit: >=10 ng/mL). Cognitive impairment was defined as a Pfeiffer Short Portable Mental State Questionnaire (SPMSQ) score <8.

Compared with the non-deficit group (n=623), the deficit group (n=129) had a lower mean SPMSQ score and more often had an SPMSQ score <8. There was no significant linear association between serum 25(OH)D concentration and SPMSQ score. However, serum 25(OH)D deficiency was associated with cognitive impairment.

Annweiler C et al. Neurology. 2010; 74(1):27-32.

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