



an Ounce of Prevention

ALZHEIMER'S PREVENTION THROUGH DELAY FALL 2009

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FEATURED ARTICLE

DISCLOSURE OF APOE GENOTYPE FOR RISK OF ALZHEIMER'S DISEASE

The e4 version (known as the e4 allele) of the apolipoprotein E (APOE) gene is known to increase an individual's risk for developing late-onset Alzheimer's disease (AD). This is true for those who inherit one copy of the APOE e4 allele as well as for those who inherit two copies of the allele who are at even greater risk. The APOE e4 allele may also be associated with an earlier onset of memory loss and other symptoms.

It is important to note that having the APOE e4 allele does not mean that person will develop AD, only that they have an increased risk of developing AD.

Genotyping of patients and their family members for APOE to assess the risk of AD is not generally recommended. This is based partly on the possibility of psychological distress that may be induced by learning of a greater risk. However, actual the impact of such knowledge has not been well studied previously.

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 either receive the results of their own APOE genotyping (disclosure group) or not (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 no significant short-term psychological risks in either groups, and test-related distress was actually 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.

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 distilling its true value.

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 \pm 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.

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.

Lu PH et al. *Neurology*. 2009; 72(24):2115-21.

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.