Research Update on Dementia and Alzheimer's Disease

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Copper and Alzheimer's Disease (AD)

There is accumulating evidence suggesting an association between copper levels in the blood and deficits of AD. In a recent report by Squitti and coauthors (Neurology, 2009; 72: 50-55), free copper levels as measured by ceruloplasmin were correlated with lower functional levels. Clioquinol, a copper chelator that may prevent copper and zinc from binding the beta amyloid, was recently found to have beneficial effects on slowing deterioration in AD. These findings suggest potentially new avenues for clinical research.

B12 and Folate Deficiencies and Dementia

Two recent studies have pointed to alternative mechanisms of how vitamin B12 and folate levels may affect the incidence of dementia (Vogiatzoglou et al: Neurology 2008; 71: 826-832; Kim et al: J Neurol Neurosurg Psychiatry 2008; 79: 864-868). One study found that patients with the lowest B12 levels had the greatest declines in brain volume.

There is a well-established association between brain atrophy and dementia. A second study found dementia was associated with greatest declines in folate and vitamin B12 levels over 2.4 years, and the relationship to baseline levels was weaker.

Statins and AD

Haag et al (J Neurol Neurosurg Psychiatry 80: 1-2, 2009) conducted a 9-year follow-up assessment of 6992 non-demented Dutch individual aged 55 and over. Those persons who had ever used a statin cholesterol-reducing medication had significantly lower risk of developing dementia, after controlling for possible confounding variables. An accompanying editorial noted that two large studies with patients with cardiovascular disease did not find a reduction in dementia and two recent studies of statin use in persons with mild or moderate AD found no significant benefits.

Cardiovascular Risk Factors and Dementia

A longitudinal study in North Manhattan (Helzner et al, Arch Neuro 2009; 66:329-335) found persons with pre-diagnosis diabetes, higher cholesterol, and higher LDL levels had greater decline in AD after diagnosis. These risk factors were thought to provide additional burden, increased oxidative stress, or trigger an inflammatory response. A second study (Kanya et al, Arch of Neurol 2009; 66: 343-348) found that non-demented men aged 70 to 79 in the upper third of body mass index showed significantly more cognitive decline whereas women did not show such a relationship. Timing may be also be important---midlife obesity (about age 50) may increase the risk of AD whereas late-life obesity (aged 65 and above) may not have as much impact.

Ginkgo Biloba to Prevent Dementia

A randomized control 6-year trial of over 3000 non-demented community volunteers (minimum age 75) found that Ginkgo biloba found no difference in the new dementia cases between placebo and ginkgo group (about one-sixth in both groups) (DeKosky et al JAMA 2008; 300: 2253-2262).

Hypertension and Late-Life Dementia

Two recent articles point to the role that hypertension plays in late-life dementia. One article(Hoffman et al: Neurology 2009;72: 1720-1726) found that persons treated for hypertension in mid-life were less demented clinically and had less AD pathology than persons who did not receive treatment or non-hypertensive. A second study (Haag et al: Neurology 2009; 72: 1727-1734) found that antihypertensive use was associated with reduction in dementia risk, especially in persons treated before age 75. Although hypertension in midlife seems to be a risk factor for cardiovascular and cerebrovascular disease in later life, in later life, low blood pressure seems to be a risk factor. Thus, there appears to be a J-shaped relationship between blood pressure and dementia. Perhaps this explains some of inconsistent findings between hypertension and dementia. Thus, in later life, may be around 75, treatment of hypertension has less value, because the balance between blood pressure, cerebral autoregulation, and brain metabolism may change. Thus, it appears that treatment of hypertension in midlife is a useful preventive strategy whereas

treatment in late life may have little or no impact on the incidence of dementia.

Predictors of Maintaining Cognitive Function in Older Adults

A recent study by Yaffe and coworkers(Neurology 2009; 72:2029-35) examined over 2500 black and white community elders over 8 years: 30% of participants maintained cognitive function, 53% showed minor decline, 16% had major cognitive decline. Significant predictors of maintenance of cognitive function included white race, high school education or higher, 9th grade literacy level or higher, weekly moderate or vigorous exercise, and not smoking. The findings show that there are many potentially modifiable factors that may reduce the chance of cognitive decline.

Donepezil (Aricept) and Galantamine (Razadyne) Treatment for Mild Cognitive Impairment(MCI)

Doody and colleagues (Neurology 2009; 72: 1555) conducted a 48-week randomized control trial of donepezil versus placebo with 821 with MCI. They found donepezil was not significant in improving the cognition and function measures used as primary end-points. Two of eight secondary measures favored donepezil, but adverse effects were nearly twice as high with donepezil than with placebo (47% vs 25%). Similarly, Winblad and coauthors (Neurology 2008; 70: 2024-35) found no difference in the 24-month conversion rate (23%) between galantamine and placebo based on studies involving 2048 subjects.

Mild Cognitive Impairment and Long-Term Outcome May Be Generally Optimistic

Manly and coworkers (Ann Neurol 2008; 63: 494-506) found that in large naturalistic follow-up study in NYC -- averaging about 3.3 to 6.7 years of follow-up in two large cohorts-- that 22% of persons with MCI developed AD, 47% remained stable, and 31% improved. Although MCI is a risk factor for AD, there are many persons who do not develop dementia.

Results of Recent Treatment Intervention Studies

1. The combination of memantine (Namenda) and a cholinesterase inhibitor (e.g. Aricept and others) was again found to be superior to monotherapy with a cholinesterase inhibitor or no treatment (Atri et al: Alz Dis Assoc Disorders, 2008; 22: 209-221).
2. Demebolin hydrochloride (an antihistamine) was found to have significant benefits in cognition over 26 weeks in Phase III trial. The results were similar to changes seen with cholinesterase inhibitors. The drug was well-tolerated with dry mouth and depressive symptoms being the most common side effects (Doody et al: Neurology 2008; 372: 207-15)
3. Post-mortem studies of 8 patients who received beta amyloid immunization showed significant increase in the clearance of amyloid (Holmes et al: Lancet 2009; 372: 216-223). The study had been terminated because of adverse effects including encephalitis. Newer studies, using different immunization strategies, are now in phase III trials.
4. Results of surgical shunt treatment that was thought to potentially clear amyloid and tau from the brain were found to produce no clinical benefits in a 215 patients (Silverberg et al, Neurology 2008; 71: 202-09).

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