Guest Editorial

Preventing Dementia: Why We Should Focus on Health Promotion Now

KEYWORDS: Alzheimer's disease; dementia; prevention; health promotion

The world's older population has been growing at a rate of 2.4% per year during the past decade, and in the year 2000 there were 580 million people aged 60 years or older (World Health Organization, 1998). With the 85 years and older group being the fastest growing segment of the population, age-related diseases and disabilities are rapidly increasing. Psychiatric morbidity is common in later life; 15% of older adults have clinically significant mental health disorders, with neurodegenerative conditions such as dementia taking the lead (Regier et al., 1998). Substantial progress has been made in the quest to unravel the pathophysiological mechanisms leading to dementia, improve the accuracy of early diagnosis, and develop dementia treatment-specific compounds. However, such developments may take decades to have a significant impact on clinical practice.

DAWN OF A NEW ERA

The past few years have produced groundbreaking discoveries in the field of dementia. Genes for autosomal dominant transmitted familial Alzheimer's disease (AD) on chromosomes 21, 14, and 1 have been discovered, as well as susceptibility genes such as the APOE ε4 allele (Tanzi & Bertram, 2001). Other loci on chromosomes 10, 12, and 9 are under investigation as potential additional causative candidate genes. These findings have limited diagnostic value, however, and no practical implications for the prevention or treatment of AD. Potential biochemical markers for AD, such as the concentration of beta-amyloid 1-42 in the cerebrospinal fluid, have been investigated, but they lack specificity and are frequently present in people who will never develop cognitive impairment (Teunissen et al., 2002).

Advances in neuroimaging techniques have improved our ability to visualize and measure the volume of brain structures, as well as their metabolic activity (Silverman et al., 2001). But again the contribution of neuroimaging to the diagnosis of dementia is at best questionable and its predictive validity unclear. Scahill and colleagues (2002) suggested that serial magnetic resonance imaging brain

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scans can distinguish subjects who will develop dementia from those who will not, but how these results would compare with "serial clinical assessments" remains to be established. It has been argued that a new era of dementia prevention is imminent and that the use of genetically engineered drugs could contribute to prevent the buildup of cerebral pathology (Bush, 2001). But do we need to wait or could this preventive era start now?

ASSOCIATION BETWEEN RISK FACTORS FOR CARDIO-VASCULAR DISEASE AND AD

Vascular risk factors are traditionally connected to the development of vascular dementia (VaD), and the call for the introduction of preventive strategies designed to reduce the risk of VaD is not new (Hachinski, 1992). By now it is well recognized that there is substantial overlap between vascular and AD pathology (Zekry et al., 2002). A more recent development is that vascular risk factors have also been associated with an increased risk of AD (de la Torre, 2002).

BLOOD PRESSURE AND DEMENTIA

Growing evidence has been accumulating of a link between high blood pressure and the development of dementia later in life (Skoog et al., 1996). In a prospective follow-up study of 167 hypertensive subjects, Tzourio and colleagues (1999) demonstrated that failure to treat hypertension was associated with increased risk of cognitive decline (relative risk [RR] = 4.3, 95% confidence interval [CI] 2.3-8.0).

In the Swedish Kungsholmen Project, 1,301 subjects aged 75 years and above were followed up for 3 years; 458 hypertensive subjects were identified, of whom 122 received diuretic treatment. The treated group had an RR of 0.6 (95% CI 0.3-1.2) of developing dementia (Guo et al., 1999). In the Honolulu-Asia aging study, Launer and colleagues (2000) showed that midlife blood pressure never treated with antihypertensive medication was associated with increased risk of AD in 3,703 Japanese American men: odds ratio (OR) = 6.6 (95% CI 2.0-21.4) for high diastolic blood pressure. Petrovitch and colleagues (2000) showed that high systolic blood pressure ($\geq$ 160 mmHg) in midlife was associated with lower brain weight and greater number of senile plaques, whereas elevated diastolic blood pressure in midlife ($\geq$ 95 mmHg) was associated with increased number of neurofibrillary tangles in the hippocampus. This finding suggests there is a direct link between high blood pressure and AD pathology. Kivipelto and colleagues (2001b) confirmed the association between midlife high systolic blood pressure and AD in the FINMONICA study and reported a similar association with mild cognitive impairment, frequently considered a predictor of AD, especially when high blood pressure was associated with elevated serum cholesterol levels (Kivipelto et al., 2001a). In another report from this study (Kivipelto et al., 2002), variables such as the APOE ε4 allele, elevated serum total cholesterol levels, and elevated systolic blood pressure in midlife were all independent risk factors for the later development of AD. Hypercholesterolemia and hypertension were associated with a higher OR (OR = 2.8, 95% CI 1.2-6.7, and OR = 2.6, 95% CI 1.1-6.6 respectively) for

AD than APOE ε4 (OR = 2.1, 95% CI 1.1-4.1). In addition, Murray and colleagues (2002) demonstrated that antihypertensive treatment reduced the odds of cognitive impairment by 38% over 5 years (OR = 0.62, 95% CI 0.45-0.84).

Promising evidence has come from prospective double-blind, placebo-controlled treatment trials of antihypertensive agents. Forette and colleagues (1998, 2002) reported a trial of 2,418 patients, aged 60 years and over, randomized to treatment with a possible combination of nitrendipine, enalapril, and hydrochlorothiazide or placebo. In 1998 the authors reported a 50% reduction in the incidence of dementia, from 7.7 to 3.8 cases per 1,000 patient-years ($p = .05$) detected with a mean treatment period of 2.0 years. In 2002, they reported results from an open-label extension phase increasing the follow-up period up to 3.9 years. Antihypertensive therapy reduced the risk of dementia by 55%, from 7.4 to 3.3 cases per 1,000 patient-years ($p < .001$). The authors concluded that treatment of 1,000 hypertensive patients with nitrendipine for 5 years would prevent 20 new cases of dementia.

STROKE AND DEMENTIA

The hypothesis that stroke could be associated not only with VaD but also with AD received strong support from the Rotterdam Study. Hofman and colleagues (1997) demonstrated that carotid artery thickening due to atherosclerosis was a strong risk factor for AD. Similar strong associations have been reported for other stroke risk factors (Kalaria, 2000). Therefore, it is not surprising that studies designed to reduce the occurrence of stroke may also reduce the incidence of dementia and AD. Both the PROGRESS Collaborative Group (2001) and the HOPE Study investigators (Yusuf et al., 2000) found that the use of angiotensin-converting enzyme (ACE) inhibitors by patients with previous strokes or transient ischemic attacks, or those at high risk for stroke, was associated with a significant decline in the incidence of strokes. Bosch and colleagues (2002) reported that significantly fewer patients treated with ramipiril developed cognitive impairment after 2 years than those treated with placebo. This effect was independent of the antihypertensive effect of ACE inhibitors (Schrader & Lüders, 2002). Early reports from PROGRESS support this finding, particularly for a reduction in cognitive impairment after stroke (PROGRESS Collaborative Group, 2003).

LIPIDS, LIPID-LOWERING DRUGS, AND DEMENTIA

In addition to the well-established relationship between elevated lipid levels and increased risk of cardiovascular and cerebrovascular pathology, lipids have additional interactions that are relevant to AD pathology, such as the effect of cholesterol on the degradation of the amyloid precursor protein and apolipoprotein E metabolism (Frears et al., 1999; Hyman et al., 2000). In a nested case-control study involving 368 practices in the UK, Jick and colleagues (2000) found that patients prescribed statins had an adjusted RR of developing dementia of 0.3 (0.1-0.6; $p = .002$). A cross-sectional population-based study from the Netherlands reported that low high-density cholesterol was associated with significantly lower Mini-Mental State Examination (MMSE) scores in 561

subjects 85 years and older (van Exel et al., 2002). A case-control approach in 492 patients with dementia and 823 healthy controls participating in the Canadian Study of Health and Aging revealed that the use of statins was associated with a reduction in the risk of AD in subjects younger than 80 years (OR = 0.26, 95% CI 0.08-0.88) (Rockwood et al., 2002). A randomized, placebo-controlled, double-blind treatment trial of 80 mg simvastatin daily for 26 weeks in 44 normocholesterolemic patients with AD reported significantly reduced beta-amyloid 1-40 levels in the cerebrospinal fluid of patients with dementia (Simons et al., 2002). MMSE scores declined significantly less among patients receiving the active treatment than in those on placebo (17.8 to 17.2 versus 17.1 to 14.4, $p < .02$). In vitro studies have shown that statins inhibit the formation of beta-amyloid in living hippocampal neurons (Simons et al., 1998), and this finding was later replicated in vivo using guinea pigs (Fassbender et al., 2001). However, it is worth noting that the doses of statins used in this experiment were much higher than those that could be safely used in humans. To date there is no substantial randomized trial evidence of efficacy of statins in either prevention or treatment of dementia or cognitive impairment.

HOMOCYSTEINE AND DEMENTIA

Data from the Rotterdam Scan Study (Vermeer et al., 2002) demonstrated that the overall risk of silent brain infarcts or severe white matter lesions is strongly associated with total homocysteine levels (OR 1.35/standard deviation [SD] increase, 95% CI 1.16-1.58). Sachdev and colleagues (2002) reported a significant

positive relationship between total plasma homocysteine levels and central brain atrophy, measured with lateral ventricle-brain ratios in the anterior ($r = .49$) and middle ($r = .43$) ventricular regions. Several epidemiological studies have shown that high plasma homocysteine is atherogenic and thrombogenic, and that reducing homocysteine with multivitamin therapy improves vascular markers such as artery intimal thickness and endothelial function (Hankey, 2002). A case-control study by Clarke and colleagues (1998) was among the first to report that older adults with high plasma homocysteine (≥ 14 µmol/L) had an increased risk of AD. The OR of confirmed AD associated with high plasma homocysteine level compared to elderly people with plasma level ≤ 11 µmol/L was 4.5 (95% CI 2.2-9.2). In a cohort study of 1,092 subjects without dementia who were followed up for 8 years, Seshadri and colleagues (2002) found that increased plasma homocysteine was a strong independent risk factor for dementia and AD; the multivariate-adjusted RR was 1.4 (95% CI 1.1-1.9) for each increase of 1 *SD* in the log-transformed homocysteine value.

DIET, SMOKING, EXERCISE, AND DEMENTIA

Diet is a potentially modifiable factor that has been directly and indirectly associated with dementia. Recent published research has focused on fat intake and its possible interaction with dementia pathology via inflammatory processes, atherosclerosis, thrombosis, and lipid metabolism in general (Grant, 1999). Barberger-Gateau and colleagues (2002) reported data from the PAQUID

study that followed up a French cohort of 1,416 older adults for up to 7 years. Participants who ate seafood at least once a week had a reduced risk of developing dementia (OR = 0.7, 95% CI 0.5-0.9). This "protective" effect was partly explained by higher education levels of seafood consumers. One hypothesis to explain this effect is that the omega-3 fatty acids contained in fish oil reduce inflammatory processes in the brain.

It has also been suggested that oxidative damage may play a central role in the pathological processes of AD and VaD (González-Gross et al., 2001). Vitamin E may reduce the progression of atherosclerosis and dementia (Sano et al., 1997), although this was not supported by a synthesis of all the studies presented in the Cochrane Review (Tabet et al., 2002). The results of the Sano and colleagues' study trial led the American Academy of Neurology (Doody et al., 2001) to recommend the use of vitamin E to slow the progression of AD. Finally, the results from a placebo-controlled, double-blind, 1-year trial of vitamin and trace-element supplementation for 86 older adults found that the cognitive scores of treated subjects improved compared to those who received placebo treatment (Chandra, 2001). Larger trials with vitamin supplementation in older adults with a longer follow-up period are under way.

Smoking is another well-recognized environmental factor for cardiovascular and cerebrovascular disease. It remains unclear, however, if smoking should also be considered a risk factor for AD. A recent systematic review of case-control and cohort studies (Almeida et al., 2002) pointed out that survival bias and other methodological problems might partly explain conflicting results, but that a restricted analysis of the studies with the most sound methodology reveals that smokers are twice as likely to develop AD as persons who never smoked (95% CI 1.3-3.0).

Laurin and colleagues (2001) explored the relationship between physical activity and cognitive impairment in 4,615 community dwellers participating in the Canadian Study of Health and Aging who were followed up for 5 years. High activity levels were associated with reduced risk of cognitive impairment (OR = 0.58, 95% CI 0.41-0.83), AD (OR = 0.50, 95% CI 0.28-0.90), and dementia of any type (OR = 0.63, 95% CI 0.40-0.98). In a longitudinal cohort study of 801 older Catholic nuns, priests, and brothers without dementia, cognitively stimulating activities were documented at baseline and the cohort was followed up for 4.5 years (Wilson et al., 2002). A 1-point increase in the cognitive activity score was associated with reduced decline in global cognition (by 47%), working memory (by 60%), and perceptual speed (by 30%), and a 33% reduction in the risk of AD (hazard ratio, 0.67, 95% CI 0.49-0.92).

CONCLUSION

The aforementioned examples are but a selected overview of an ever-increasing number of potentially modifiable risk factors of dementia that also include diabetes mellitus, head injury, sex hormones, and education. There seems to be no reason to delay the immediate evaluation of health promotion strategies specifically designed to reduce the risk of cognitive impairment in later life (see Table 1). These programs could include (a) primary prevention starting

TABLE 1. Examples of Potentially Modifiable Risk Factors for Dementia and Potential Health Promotion Strategies

Risk Factor	Strategy
• Hypertension in midlife	• Antihypertensive medication
	• Decreased salt intake
	• Physical activity
• Stroke	• Hypertension treatment
	• Diabetes treatment
	• Smoking cessation
	• Use of ACE inhibitors
	• Physical activity
• Hyperlipidemia	• Diet (vegetables, lean meat, low-fat milk, avoid consumption of animal-derived fat, etc.)
	• Lipid-lowering agents, particularly statins
	• Physical activity
• Smoking	• Smoking cessation
• High plasma homocysteine	• Vitamin B_{12} and folate intake
• General health measures that seem to reduce the risk of AD	• Physical activity
	• Seafood intake
	• Use of antioxidants such as vitamin E
	• Participation in cognitively stimulating activities

Note. ACE = angiotensin-converting enzyme; AD = Alzheimer's disease.

in midlife and (b) secondary prevention in subjects with memory complaints and mild cognitive impairment in later life (Cooper, 2002). We should attempt to attain a level of clinical practice where the prevention of cognitive impairment and dementia in later life is considered as important as preventive strategies for cardiovascular diseases and stroke. Because these conditions share common risk factors, a combined practical implementation of health promotion programs should be a realistic and affordable goal.

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