

Stroke, Cognitive Decline and Vascular Dementia: The Silent Epidemic of the 21st Century

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Twenty years ago, voices of alarm began to be heard in the health community addressing the problem of the silent epidemic of dementia in the elderly, the most common and unwanted accompaniment of increased longevity [1, 2]. Today, Alzheimer's disease (AD) is no longer a silent problem. It has become a household name, a common condition affecting old people the world over. In most instances, AD is now readily recognized, accurately diagnosed and appropriately treated.

However, predictions for the future remain grim. In 1997, the prevalence of AD in the United States of America (USA) was 2.32 million (range: 1.09 to 4.58 million), with an incidence of 360,000 new cases per year [3]. Current estimates for the USA indicate that at the current rates the disease will quadruple in 50 years: by 2050 there will be between 7.98 and 12.95 million people suffering from AD [4], afflicting 1 in 45 Americans. A similar situation is occurring in developing and developed nations worldwide. A Public Health intervention that could delay the onset of AD by 2 years, would decrease by 20% the number of prevalent cases expected by 2050 [3].

The greatest hope for the prevention of AD comes from recent neuroepidemiological evidence indicating that a number of vascular risk factors appear to increase the risk of AD later in life [5, 6]. The most important vascular risk factors for AD are midlife hypertension [7–10] and diabetes mellitus [11]. The exact mechanisms of

action are not clear but untreated hypertension clearly increases the risk [8]. Furthermore, the results of controlled clinical trials indicate that treatment of systolic hypertension in the elderly decreases by 50% incident cases of both vascular dementia (VaD) and AD [12].

Another important vascular risk factor for AD is hyperhomocysteinemia. Data from the Framingham study showed that increase in plasma homocysteine over $14 \mu\text{M}$ nearly doubled the risk of AD [13]. Furthermore, the severity of cerebral atrophy worsens at higher concentrations of homocysteine [14–17], and with low serum folate [18].

Normally, homocysteine levels increase with age; decrease in plasma levels occurs via metabolic pathways mediated by folate, vitamin B₁₂ and vitamin B₆ as cofactors. Dietary supplementation with 400 μg of folic acid per day decreases levels of homocysteine by 2–5 μM in most subjects [19]. Of some concern is the fact that supplementation with folic acid causes a shift in dependency from folate to vitamin B₁₂ [20]; excessive intake of folic acid may possibly mask vitamin B₁₂ deficiency [21].

It must be emphasized that by age 65 as many as 50% of the elderly are no longer able to absorb the vitamin B₁₂ in food [21–24] due to lack of transcobalamin (TC). Haptocorrin and TC are the two main serum binding proteins for cobalamin (Cbl), but TC is responsible for delivery of the TC-Cbl complex to receptors on the cell surface of eve-

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ry DNA-synthesizing cell in the human body [25]. In the elderly, therefore, dual supplementation with vitamin B₁₂ and folate may be required [20, 22].

Since 1998, folic acid has been added to enriched grain products in the USA, primarily for prevention of neural tube defects (NTD). Fortification adds 100–240 µg of folic acid to the daily diet [26] and has resulted in a 19% reduction of NTD prevalence in the USA [27]. Numerous other countries have recently adopted dietary fortification with folic acid [28–31].

An additional benefit of increasing folate consumption is a decrease in the risk of occlusive vascular disease and stroke associated with elevated homocysteine [22, 32, 33]. Folate improves vascular endothelial function by mechanisms probably independent of homocysteine effect in patients with coronary artery disease [34], and decreases the rate of restenosis after coronary angioplasty [35]. Homocysteine damages the endothelium by an oxidative effect; therefore, some of the protection from AD afforded by dietary consumption of antioxidants [36] could be mediated by prevention of the deleterious effects of hyperhomocysteinemia.

Stroke and Ischemic Heart Disease: The Global Magnitude of the Problem

Ischemic coronary artery disease (CAD) and stroke are, respectively, the two leading causes of mortality and morbidity in the elderly. The magnitude of the problem is astounding [37]: in the USA there are 12.6 million people with history of myocardial infarction (MI), angina, or both, for a prevalence of 6.3 million hospital discharges for treatment of CAD and 1 million for congestive heart failure (CHF). There are 1.1 million incident cases of MI per year and 550,000 annual cases of CHF. There are more deaths from CAD and CHF than from all forms of cancer combined. CAD is a disease of aging, showing a prevalence of 1% in the age group 50–59 years and increasing tenfold to >10% after the age of 80 years.

Cerebrovascular disease (CVD), including stroke, is currently the second cause of death worldwide and the commonest cause of chronic disability. The frequency of CVD also rises exponentially with age. There is a 100-fold increase in stroke incidence from age 30–40 to age 80–90 (i.e., from 3/10,000 to 300/10,000) [38]. This is particularly pertinent considering that people 85 years of age and older are the fastest growing segment of the population.

According to the World Health Organization's Global Burden of Disease study [39], by the year 2020 ischemic

CAD and CVD will remain the leading non-infectious causes of disease burden in adults, as measured in DALYs (Disability Adjusted Life Years). Hypertension, tobacco and physical inactivity appear to be the main preventable risk factors [39].

Stroke, CVD and CAD Causing VaD: The Incoming Silent Epidemic

Although the impact of CAD and CVD as major causes of death and physical disability are readily recognized, their contributions to cognitive dysfunction and dementia are almost totally unrecognized. For instance, post-stroke dementia, also known as multi-infarct dementia when it develops as a result of multiple strokes, affects about 30% of patients older than 65 years after ischemic stroke [40–42]. This means that in the United States alone, the incidence of post-stroke VaD is approximately 125,000 new cases per year (about 1/3 of the estimated 360,000 incident cases of AD). In Europe, an estimated 2,700,000 persons have suffered at least one stroke, with 536,000 new stroke cases per year [43] for an estimated incidence of 140,000 annual cases of post-stroke VaD. It is anticipated that the figure for Latin America and Japan would be at least similar or higher [44]. A recent study from the Rotterdam cohort [45], demonstrated the importance of silent strokes as RFs for dementia in the elderly. Silent, subcortical strokes, particularly in the thalamus, produced significant cognitive decline and more than doubled the risk of dementia (hazard ratio, 2.26; 95% confidence interval, 1.09 to 4.70).

Hypoperfusion from CHF is being increasingly recognized as a significant factor for cognitive decline in the elderly. A large study recently demonstrated cognitive impairment in 26% of patients discharged from the hospital after treatment of CHF [46]. Worse cognitive function occurred in cases with poor left ventricular function and lower systolic blood pressure, indicating that cerebral hypoperfusion is an important factor [47] in this cardiogenic form of VaD, although CHF also increases the risk for cerebral embolism. Other populations at risk of unrecognized VaD include patients post coronary artery bypass graft (CABG), as well as those in cardiac rehabilitation facilities and in convalescence services after major surgery, in particular following hip fracture repair and knee replacement. It has been predicted that VaD resulting from CAD, CHF and CVD may be the most common form of dementia in the elderly [48]. This will become, most certainly, the silent epidemic of the 21st century.

In keeping with the importance of the problem, this issue of *Neuroepidemiology* is devoted in its entirety to stroke, presenting articles from widely separated areas of the world: Brazil, Malaysia, and Finland, also including a study of post-stroke cognitive decline and VaD from Sydney, Australia [49]. Finally, an important article by Ingles and her colleagues from the Canadian Study on Health and Aging [50] points to the importance of appropriate

neuropsychological tests in the elderly in order to recognize the presence of underlying cognitive decline and dementia.

Control of cardiovascular risk factors is probably our best chance of fighting AD and the incoming epidemic of VaD. However, it must be remembered that prevention of dementia must begin no later than midlife.

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