Prevention of dementia should start 20 years before symptoms become apparent

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This editorial refers to ‘Predictive utility of the Framingham general cardiovascular disease risk profile for cognitive function: evidence from the Whitehall II study’ by F. Kaffashian et al., on page 2326.

Modern medicine has made tremendous progress. The consequence is a steep increase in life expectancy, not only in developed countries, but also in countries such as India and China. Mortality and morbidity of major vascular diseases such as myocardial infarction and stroke are improving in individual patients. Increasing age in a population leads to an almost exponential increase in the prevalence of dementia. Dementia will be the major issue for the next 50 years to come, on the level of both the individual and his or her caregivers and social and medical systems.

Alzheimer’s disease is the most common cause, followed by vascular dementia. Vascular dementia is a small vessel disease of the brain, with diabetes mellitus and untreated hypertension as the most frequent aetiological factors. The typical clinical appearance of vascular dementia is the combination of cognitive deficits with gait apraxia and incontinence. Magnetic resonance imaging (MRI) of the brain shows lacunar infarcts and deep white matter lesions. Originally Alzheimer’s disease was supposed to be a pure neurodegenerative disease. In recent years it has become apparent that vascular factors play an important role in the pathophysiology of Alzheimer’s disease. In addition there is a considerable overlap of vascular and degenerative mechanisms in the pathophysiology of dementia. Figure 1, taken from Humpel (2011), illustrates the relationship between vascular and non-vascular mechanisms of Alzheimer’s disease.

Mild cognitive impairment has been identified as a major predictor of dementia. The study by Kaffashian et al. adds important information to the question of how frequent mild cognitive deficits occur in middle-aged persons and whether these changes are related to major vascular risk factors. In a longitudinal British cohort study they investigated 4827 individuals, mean age 55 years, and assessed vascular risk factors by means of the Framingham General Cardiovascular Risk Profile and cognitive function by validated instruments. Baseline examinations took place during 1985–1988 and cognitive tests were introduced between 1997 and 1999 and repeated in 2002–2004 and 2007–2009. Beyond all finesse of statistical analyses, the result was very obvious: a 10% increment in the cardiovascular risk score was associated with a poorer performance in all cognitive domains. This was true for women and men. In addition, higher cardiovascular risk was associated with a greater 10 year cognitive decline in men. These results are in line with another study which showed that vascular risk factors present at mid-life are strong predictors of dementia later in life.

What are the consequences of this study? The results clearly indicate that we should not wait to identify possible vascular risk factors in the population until people reach retirement age. Prevention programmes need to start at age 50 at the latest. Vascular risk factors need to be not only identified but also treated. The willingness to do so and compliance and adherence with medical and non-medical approaches are poor in most countries. At present we tell persons with vascular risk about the risk of myocardial infarction and stroke. In future we should also tell them that vascular risk factors are also risk factors for cognitive decline and most probably dementia.

The missing scientific link, however, is the proof that dementia can be prevented or delayed by the treatment of vascular risk factors. Large-scale randomized, placebo-controlled trials would need an observation time of 5–10 years in order to show a positive result. Most recent trials with antihypertensive drugs or statins were neutral, which most probably was due to too short an observation period. Only the Systolic Hypertension in Europe study (Syst-Eur) has shown an effect of treating elevated blood pressure in subjects over the age of 60 years on dementia.

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Figure 1. A common unifying hypothesis for Alzheimer’s disease. It is hypothesized that chronic mild exposure to different (vascular) risk factors may play a role in the development of Alzheimer’s disease. These factors are, for example, hyperhomocysteinaemia, hypercholesterolaemia, or type 2 diabetes. This leads to damage of the neurovascular brain capillaries, leading to silent strokes and to acidic conditions (1) or to a dysregulation of β-amyloid at the blood–brain barrier, resulting in increased β-amyloid (1–42) levels in the brain (2). The cerebrovascular dysfunction may result in damage of the sensitive neurovascular unit (3). The subsequent retrograde-induced cell death of cholinergic neurons correlates with the lack of cortical or hippocampal acetylcholine (4). Metabolic disturbances (e.g., enhanced influx of toxic compounds, enhanced efflux of metabolic waste, or reduced energy supply) may induce neuroinflammation (5) and microglial activation and reactive gliosis (6). Different risk factors (such as metals, reduced pH, or reduced transport or degradation of β-amyloid) may result in aggregation of β-amyloid and plaque deposition (7). The cerebrovascular damage and dysfunctional β-amyloid clearance result in deposition of β-amyloid (angiopathy) in brain vessels (8). It is suggested that metabolic disturbances cause an imbalance of specific protein kinases (PK) or phosphatases (PP), resulting in abnormal tau phosphorylation, which finally causes the tau pathology (9). Microglia inflammation enhances matrix metalloproteinase-9 (MMP9) and causes a dysfunction of the metabolism of nerve growth factor (NGF) with a reduced bioavailability for cholinergic neurons, supporting their cell death (10). Tau pathology may, on the other hand, also be caused by β-amyloid plaque deposition (11) or may contribute to neuronal cell death (12). Reprinted from Exp Gerontol 2010, 46/4, Humpel C. Chronic mild cerebrovascular dysfunction as a cause for Alzheimer’s disease?, pp. 225–232, Copyright (2010), with permission from Elsevier.10.1016/j.exger.2010.11.032.


In a pinch

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A 38-year-old woman presented with progressive exertional chest tightness. She had a history of an unrepaired secundum atrial septal defect and Eisenmenger’s syndrome with severe pulmonary hypertension. Echocardiogram (Panel A) revealed right ventricular hypokinesis, right ventricular enlargement with flattening of the interventricular septum (arrow), and a right ventricular systolic pressure of 120 mmHg. Initial coronary computed tomographic angiography (CTA) findings included a dilated pulmonary artery trunk (46 mm), a calcium score of 0, and normal coronary arteries. She was discharged home shortly, but the discrepancy between her symptoms and the CTA interpretation prompted further physician review of her CTA which suggested posterior displacement of and compression of the ostial left main coronary artery (LMCA) as it coursed between the aortic root and the enlarged pulmonary artery (Panel B, arrow). Invasive coronary angiography demonstrated an 80% eccentric stenosis of the ostial LMCA (Panel C). Intravascular ultrasound revealed slit-like stenosis of the ostial LMCA with pulsatile, extrinsic compression by the enlarged pulmonary artery (Panel C, insert). The patient was too high risk for coronary artery bypass surgery due to her underlying pulmonary hypertension and right ventricular dysfunction. Direct stenting of her ostial LMCA using a 5.0 × 16 mm Liberte™ (Boston Scientific, Natick, MA, USA) bare metal stent resulted in 0% residual stenosis (Panel D), TIMI-3 flow, and resolution of her symptoms. Six months later, she was angina-free and coronary angiography revealed a widely patent LMCA stent.

All authors contributed to patient management and the writing of the report. Written consent was obtained.

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