William M. Feinberg Lecture: Cognitive Vitality and the Role of Stroke and Cardiovascular Disease Risk Factors

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Background and Purpose—Vascular risk factors are common in the elderly, and some such as hypertension may be important predictors of cognitive impairment.

Summary of Review—In this article, the role that vascular risk factors may play in the prevention of vascular and nonvascular forms of cognitive impairment is reviewed.

Conclusions—Because vascular risk factors may have negative effects on brain structure and cognitive function, and because vascular risk factors may be present in midlife or possibly earlier, we may need to develop long-term intervention strategies to control or prevent vascular risk factors in an effort to preserve cognitive vitality as we age. (Stroke. 2005;36:875-879.)

Key Words: cognitive disorders ■ risk factors ■ vascular disorders

The brain is truly a treasure to protect. It is a master organ containing programs for our cognitive abilities and the concepts of self and awareness. It is estimated that the cerebrum contains >20 billion neurons, and ~25% of human genes are expressed in the brain. As we age, the focus for many of us is to remain healthy, and the importance of protecting the brain becomes a priority. For those of us who wish to age gracefully, many are pondering what may be in store for us in the future. Do we wish to live to be 100 years or older? Will we be wiser or healthy in old age? Are we adding “life to years” or “years to life?” What are some of the secrets of successful aging and outliving aging-associated fatal illness? Is there a fountain of youth, or should we be taking a “Polypill” to protect ourselves from myocardial infarction, stroke, and the devastating complications of these diseases? Will programmed cell death or negative gene–environmental interactions overcome us? Successful aging may not be a simple proposition.

Stroke and cardiovascular disease risk factors are common in the elderly population as are stroke and cognitive impairment. The former factors could play a role in how successfully our brain ages and determine, at least in part, whether we are free of cognitive impairment and physical disability. Recent studies suggest that the ravages of stroke and cardiovascular disease risk factors may not be limited only to vascular forms of cognitive impairment but might also be linked to Alzheimer disease, the leading irreversible cause of dementia in most regions of the world. Therefore, our ability to treat vascular risk factors and possibly prevent them provides hope that we might be able to prevent or at least slow 2 of the leading causes of dementia. In this review, select examples of successful aging and the role that stroke and cardiovascular disease risk factors might play in the prevention of vascular and nonvascular forms of cognitive impairment are discussed.7

Examples of Successful Aging

Aging does not inevitably result in cognitive decline and physical disability. Some persons live to old age without major disabilities. Several illustrative examples of successful aging are reviewed. The review is not meant to be exhaustive but rather to demonstrate a spectrum of factors that might be involved in successful aging. Central to successful aging, so it seems, is a protective vascular risk factor profile and protective genetic factors.

Japanese Hawaiian Men

The Honolulu-Asia Aging Study provides measures of physical, mental, and sensory function. Originally, the cohort comprised 8006 men of Japanese ancestry who were born during the years 1900 to 1919 and lived on the Island of Oahu, Hawaii in 1965. Baseline examinations were conducted from 1965 to 1968 when the men were 45 to 65 years of age. The fourth examination was conducted between 1991 and 1993.

Longitudinal follow-up showed that there were 3263 survivors of which 41% remained free of major clinical illness; 40% remained free of physical and cognitive impairment; and 19% remained free of illness and impairment. Consistent predictors of healthy aging were low blood pressure, low...
serum glucose, not smoking cigarettes, and not being obese. The authors concluded that much of disability and illness of the elderly was related to risk factors present in midlife.

**Ashkenazi Jews**

Persons with exceptional longevity may have a lower incidence or significant delay in the onset of age-related illness. Furthermore, their family members may have biological factors that alter aging processes and disease susceptibility.

Some Ashkenazi Jews have both cultural and genetic homogeneity that may make this group advantageous to study in gene identification research. In a case-control study primarily featuring Ashkenazi Jews, individuals with exceptional longevity and their offspring were found to have significantly larger high-density lipoprotein and low-density lipoprotein particle size; lower prevalence of hypertension, cardiovascular disease, and the metabolic syndrome; and increased homozygosity for the 1405V variant in cholesteryl ester transfer protein, which is involved in the regulation of lipoprotein and its particle sizes. The authors concluded that lipoprotein particle sizes may be heritable and promote healthy aging.

**Centenarians**

The phenomenon called demographic selection means that certain persons are less likely to have environmental and genetic exposures that lead to death at earlier ages. Centenarians are such a group and exemplify, for example, rare occurrence of the apolipoprotein E e4 allele that is associated with heart disease and Alzheimer disease. Exceptional longevity has been linked to a familial component.

Furthermore, the children of centenarians may have substantially reduced risks of age-related diseases such as heart disease, hypertension, and diabetes mellitus. A locus on chromosome 4 may be associated with exceptional longevity. However, both the degree of neuropathology and brain resistance to the expression of the neuropathology may be important for predicting whether cognitive impairment will or will not occur in the elderly. Additional study is needed to determine whether longevity is separated from diseases that accompany it.

**Alzheimer Disease and a Shift in the Dementia Paradigm**

The Nun Study findings that the severity and frequency of dementia among those with Alzheimer disease pathology was greater when there were small deep infarcts sparked renewed interest in the possible importance of cerebrovascular disease in the dementias of the aged. Stroke, like Alzheimer disease, is common in the elderly. However, when there is cognitive impairment in an elderly person after stroke, some believe that the occurrence of stroke is either an innocent bystander, a process that unmasks Alzheimer disease, or one that contributes to mixed Alzheimer and vascular dementia.

In Alzheimer disease, the presence of brain vascular pathology such as abnormal vascular basement membranes and coiling of microvessels supports a possible contribution of vascular disease to the pathophysiology of degenerative dementia. An angiogenesis hypothesis has been developed whereby injury or dysfunction to the endothelium of brain blood vessels is thought to lead to local thrombus formation and subsequent release of amyloid precursor protein (APP) and a toxic peptide. APP could then lead to amyloid plaque formation and the toxic peptide to neuronal dysfunction or death. Then, production of oxygen free radicals could result in further endothelial cell dysfunction or damage and more APP and toxic peptide release.

Therefore, in Alzheimer disease it is hypothesized that pathological angiogenesis or neovascularization may occur in response to impaired cerebral perfusion and vascular injury (inflammation) and leads to morphological (eg, capillary density, vascular loop formation) and biochemical changes (eg, expression of vascular endothelial growth factor, transforming growth factor-β, and tumor necrosis factor-α) that activate Alzheimer disease pathology.

Although there continues to be controversy about the role of cerebral infarcts in the Alzheimer process, it has been hypothesized that there may be converging pathogenic mechanisms in vascular and neurodegenerative forms of dementia.

Accordingly, a synergism may occur as vascular dysregulation may be mediated by β-amyloid protein, and cerebral ischemia may increase the production of APP and thereby increase the formation of β-amyloid. Therefore, vascular dysregulation related to β-amyloid and cerebral ischemia increasing APP and subsequent β-amyloid formation could result in synergism of the vascular and degenerative pathophysiologic processes. We have reviewed experimental and clinical data to support such a synergism in a previous article.

Based on these proposed mechanisms and other data, our conceptualization about Alzheimer disease has expanded and is now perceived as a more heterogeneous one. Then, what might be the role of stroke and cardiovascular disease risk factors in conferring risk for cognitive impairment in the elderly?

**The Role of Stroke and Cardiovascular Disease Risk Factors on Cognitive Function**

**Vascular Cognitive Impairment**

It has been assumed that risk factors for vascular cognitive impairment (VCI) will be the same as those for stroke. We tested this hypothesis in a hospital-based case-control study of ischemic stroke patients designed to elucidate why some ischemic stroke patients do or do not have cognitive impairment develop. VCI takes into account a spectrum of cognitive impairment from mild to more severe (ie, the full-blown state of vascular dementia). In our study, cases were defined as those with ischemic stroke and dementia, and controls were those with ischemic stroke but no dementia. We performed multiple logistic regression analysis and found that the following factors were predictors of dementia associated with multiple cerebral infarcts: age, lower educational attainment, history of myocardial infarction, and recent cigarette smoking. History of hypertension was predictive of vascular dementia in one multivariable model; however, when we
controlled for education, there was no longer a statistically significant association. We also found that systolic blood pressure level was negatively associated with case status to suggest that once dementia was present, it might be advantageous to allow the blood pressure to remain elevated to some degree rather than aggressively lowering it in an older person.

In a companion cranial computed tomography study, we found that left cortical infarcts and diffuse enlargement of the left lateral ventricle were predictors of vascular dementia. Finally, in a second and separate neuroimaging study that assessed computed tomography and magnetic resonance imaging findings among black subjects with Alzheimer, vascular dementia, and stroke without dementia, the presence of white matter lesions, nonlacunar infarcts, and left subcortical infaracts on computed tomography were predictors of vascular dementia when compared with Alzheimer disease, and widening of the third ventricle and right hemisphere infarcts on magnetic resonance imaging were neuroimaging predictors of vascular dementia when compared with Alzheimer disease.

Later, I performed a review of risk factors for vascular dementia and graded the available data according to the quality and strength of evidence rating. The review focused on 4 major categories of risk factors, ie, demographic, atherosclerotic, genetic, and stroke-related, and netted the following results. Demographic factors for vascular dementia were age, male sex, and lower education attainment. The atherosclerotic risk factors were history of hypertension, cigarette smoking, myocardial infarction, diabetes mellitus, and lipids. Genetic factors were cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL) and possibly the APOE e4 allele. The stroke-related factors were volume of cerebral tissue loss, evidence of bilateral cerebral infarction, strategic infarction, and white matter disease. Silent cerebral infarction and ventricular size might also play a role in conferring vascular dementia risk. Of the different factors, the available data were most compelling for age (Quality of Evidence Rating Class [QERC] II, Strength of Evidence Rating Type [SERT] A) and hypertension (QERC II, SERT B) as risk factors for vascular dementia.

Other Studies on Cognitive Impairment and the Role of Vascular Risk Factors
A number of major observational epidemiological studies have helped to clarify the role of vascular risk factors on dementia or cognitive impairment in general or on a specific disease. Recently, I reviewed these studies and reported the major findings. Key messages from these studies regarding vascular risk factors and cognitive impairment are: (1) systolic and diastolic hypertension may be associated with risk of developing dementia; (2) systolic hypertension in midlife may be associated with risk of cognitive decline later in life, as well as larger volumes of white matter lesions and smaller brain volume; (3) untreated or poorly treated hypertension or hypertension with hyperinsulinemia may be associated with risk of poorer cognitive function; (4) smoking during midlife may be associated with risk of cognitive dysfunction later in life; (5) elevated low-density lipoprotein cholesterol may be associated with risk of vascular dementia, and monounsaturated fat and fish consumption may protect against cognitive impairment, as may vitamin E and a Western diet protect against VCI (in Japanese Hawaiian men); and (6) diabetes mellitus, atrial fibrillation, systemic markers of atherosclerosis, and homocysteine may be important in conferring risk of cognitive impairment.

Casserly and Topol have identified common genetic and environmental risk factors that may link atherosclerosis to Alzheimer disease. The factors common to the 2 conditions include the APOE e4 allele, hypercholesterolemia, hypertension, hyperhomocysteinemia, diabetes mellitus, metabolic syndrome, systemic inflammation, smoking, increased fat intake, and obesity. Sex hormones might also be added to the list.

Casserly and Topol recommend study of cardiovascular drug classes to attempt to thwart Alzheimer disease. Drugs that might be considered for testing (some of which are being tested or have already completed at least preliminary testing) are drugs that influence cholesterol homeostasis and those that have anti-inflammatory properties, anti-angiogenic properties, and amyloid β effects. Hormone replacement therapy and anti-inflammatory drugs, thus far, have not been shown to be beneficial for the preservation of cognition though experimental models and observational epidemiological studies would have predicted otherwise. Reasons for the apparent failure of these drugs are reviewed elsewhere.

The impact of vascular risk factors on brain structure and cognitive function has been reported by the Framingham investigators. They show that 10% increments in 10-year risk of stroke according to the Framingham Stroke Risk Profile is associated with performance decrements in multiple cognitive domains such as visual–spatial memory, attention, organization, scanning, and abstract reasoning. The same investigators reported previously that vascular risk factors were associated with smaller brain volumes based on a monotonic-type curve demonstrating smaller brain volumes as the vascular risk factor burden increased.

Strategies to Preserve Cognitive Vitality
Strategies to achieve and maintain cognitive vitality have been summarized previously. These recommendations originated from a workshop, “Achieving Cognitive Vitality with Aging,” that was held at Canyon Ranch Health Resort in Tucson, Arizona, May 2 to 4, 2000. As one might anticipate based on this discussion, this guide recommends avoidance of smoking and heavy alcohol use and proper management of medical comorbidities such as hypertension, diabetes, and hypercholesterolemia. In addition, given the possible protective effect of mental and physical exercise, social engagement, stress reduction, and proper nutrition for cognitive vitality, these factors are promoted to achieve cognitive vitality. Finally, clinical trials of various therapeutics such as cognitive enhancers and protective agents are advocated.

We have begun to study a population of persons who are at high risk for cognitive impairment and stroke based on their black race–ethnic status but who belong to the Seventh-Day Adventist Church and practice many of the aforementioned strategies for maintaining cognitive vitality based on church doctrine. Adventist lifestyle and other practices offer a
unique opportunity to study diet and the influences of other healthful lifestyle factors, genetics, and spirituality on the risk of cognitive impairment.

Conclusion

Vascular risk factors may have measurable negative effects on brain structure and cognitive function. The window of opportunity to intervene on some of these factors may extend to as early as midlife or possibly earlier. This means that we may need to develop long-term intervention strategies. Hypertension in relation to cognitive dysfunction has a high estimated population attributable risk and therefore is an obvious target for intervention as we strive to preserve cognitive vitality. Previous studies have shown that use of blood pressure-lowering agents may reduce both vascular and Alzheimer-type dementias or cognitive impairment or decline. Cognitive function, however, has not been the primary outcome of these clinical trials.

Hypertension may be linked to cognitive impairment by a number of mechanisms, including stroke with strategically located infarcts (eg, thalamus, subfrontal cortical areas) or silent infarcts, induction of white matter disease, induction of brain atrophy, endothelial dysfunction, via activation of the renin-angiotensin system or by other mechanisms.

Eventually, we may be able to manipulate or prevent brain β-amyloid deposition, which is believed to be important in the pathogenesis of Alzheimer disease. Another avenue for possible vascular prevention of cognitive decline rests in the brain’s handling of glucose and insulin and how these substrates may be linked to β-amyloid flux.

We are challenged to develop and test new interventional hypotheses focused on vascular risk factors as they relate to preserving cognitive vitality. These strategies may afford the opportunity to reduce the global burden of VCI and Alzheimer disease.

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References


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