Risk Factors for Vascular Dementia and Alzheimer Disease

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Abstract—Alzheimer disease and vascular cognitive impairment are important causes of cognitive decline in the elderly. It has now been shown that vascular risk factors have measurable negative effects on the brain and are associated with cognitive impairment. We review vascular factors that might be responsible to cognitive decline in Alzheimer disease and vascular cognitive impairment and the corresponding interventions that might prevent cognitive impairment as we age. (Stroke. 2004;35[suppl I]:2620-2622.)

Key Words: Alzheimer disease  ■  cognitive disorders  ■  risk factors

Alzheimer disease (AD) and vascular cognitive impairment (VCI) are estimated to be the number one and two leading causes of irreversible cognitive impairment of late life, respectively. VCI is a relatively new nosological term that takes into account the spectrum of severity of cognitive impairment associated with vascular disease (eg, mild, moderate, and severe, or the full-blown state called vascular dementia); the underlying pathophysiological mechanism (eg, subcortical ischemic vascular disease, amyloid angiopathy, cortical infarction, etc.); and the potential for intervention and prevention based on the pathophysiological mechanism of the “brain-at-risk” stage. Because both AD and stroke show an exponential increase in frequency with age, AD and VCI may coexist as a mixed form of cognitive impairment or the existence of stroke may unmask or potentiate AD. It has been hypothesized that there may be a synergism between AD and stroke pathogenic mechanisms. Cerebral ischemia and amyloid may synergize to produce AD and vascular changes in the brain. Furthermore, an angiogenesis hypothesis has been proposed, which links the two pathophysiological processes. However, in a recently published neuropathological study, cerebral infarctions were shown to independently contribute to the likelihood of dementia but did not interact with AD pathology to increase the likelihood of dementia beyond their additive effect.

It has become apparent that AD might be a heterogeneous disorder now that vascular risk factors and atherosclerosis have been associated with AD. Whether this link represents a toxic effect of vascular factors on the microvasculature of susceptible brain regions, some other process, or that atherosclerosis and AD are independent but convergent disease processes remains uncertain. The treatment of one of the important atherosclerotic vascular risk factors, hypertension, has been shown to reduce the risk of dementia including AD or vascular and mixed dementias. Furthermore, some major midlife vascular risk factors have been linked to cognitive impairment later in life. In this paper we will review the status of risk factors for VCI and AD and the evidence for the borderland of shared vascular risk factors that may be important for prevention efforts.

Risk Factors for VCI

In comparison to AD, VCI has been relatively understudied. Problems with operationally defining VCI, proving that AD was not the dominant form of cognitive impairment in an elderly patient with stroke, and a shift of interest and resources to the study of AD have been some of the problems that have plagued the field of VCI. It has been assumed that risk factors for VCI would be the same as those for stroke. An evidence-based review that I carried out in 1997 confirmed this impression. Risk factors for vascular dementia were divided into 4 major classes: demographic, atherosclerotic, genetic, and stroke-related. The demographic risk factors turned out to be age, male sex, and lower educational level. The major atherosclerotic risk factors were history of hypertension, cigarette smoking, myocardial infarction, diabetes mellitus, and hyperlipidemia. The genetic factors included such familial vascular encephalopathies as cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL) and possibly apolipoprotein (apoE) 4. The stroke-related factors were volume of cerebral tissue loss, evidence of bilateral cerebral infarction, strategic infarction (eg, thalamic, angular gyrus, or subcortical frontal infarction), and white matter disease. Silent cerebral infarcts, cerebral atrophy, and ventricular size were also believed to play a role in heightening risk of VCI.

Risk Factors for AD

In the US and Europe, AD is the most common form of irreversible dementia of late life. It is estimated that the prevalence is around 1.5% at age 65 years and doubles every 4 years to reach about 30% at age 80 years. The incidence of...
AD increases with age and is about 1% per year but may be lower in men and in persons of African and Asian descent. However, it has been reported that VCI may be more prevalent than AD in some Asian countries.

Early-onset AD cases are uncommon and make-up about 6% to 7% of all cases. About 7% of early-onset cases are familial. These latter cases generally follow an autosomal dominant form of inheritance. Family linkage studies and DNA sequencing point to mutations including the gene encoding β-amyloid precursor protein on chromosome 19, presenilin 1 (PSEN1) on chromosome 14, and presenilin 2 (PSEN2) on chromosome 1. In the case of these 3 gene mutations, AD appears to result from increased production of AB42. These mutations can shift the cleavage site to favor the gamma-secretase site and increased production of the toxic AB42 over the less toxic AB40 peptide.

Beyond age, risk factors for AD have remained elusive. Dementia in a close family member and the ε4 allele of the apoE susceptibility gene have been confirmed as risk factors. Lower levels of education have also been associated with AD; however, it has been unclear whether this is attributable to poor compensatory strategies that hasten recognition of the disease or, for example, to adverse exposures earlier in life that might heighten risk of dementia. Other factors such as female sex, infection of various types, lipid concentrations, history of head injury, head circumference, and hormone replacement therapy (HRT) might be factors that interact with apoE genotype to modify disease risk. Thyroid dysfunction and preceding history of depression have also been associated with dementia in observational epidemiological studies.

A new focus of study in AD has been atherosclerotic vascular risk factors and the corresponding interventions that might reduce risk. There are many notable observational epidemiological studies that have helped clarify the role of vascular risk factors in AD. These include but are not limited to the Honolulu Asia Aging Study, the Goteborg study of 70 year olds, the National Heart, Lung, and Blood Institute Twin Study, studies in Uppsala, Sweden and Kuopio, eastern Finland, the Zutphen Elderly Study, the Rotterdam Study, the Italian Longitudinal Study on Aging, the Washington Heights Columbia Aging Study, the Framingham Study, the Nun Study, the Chicago Health and Aging Project, and the Bronx Aging Study. These studies have highlighted the possible role of hypertension, diabetes mellitus, smoking, lipids, hyperinsulinemia, homocysteine, physical inactivity, fat intake and possible protective dietary factors (eg, fish consumption, vitamins E and C), atrial fibrillation, systemic markers of atherosclerosis, and other vascular factors that may increase or decrease risk of cognitive impairment, AD, or VCI.

Casserly and Topol have summarized common genetic and environmental risk factors for AD and atherosclerosis: apoE ε4 polymorphism, hypercholesterolemia, hypertension, hyperhomocysteinemia, diabetes mellitus, metabolic syndrome, smoking, systemic inflammation, increased fat intake, and obesity. They list cardiovascular drugs with potential therapeutic benefit in AD based on the following mechanisms: cholesterol homeostasis, antiinflammatory properties, antiangiogenic properties, and AB effects. The cardiovascular drugs with possible beneficial effects in AD include angiotensin converting enzyme inhibitors, angiotensin II blockers, peroxisomal proliferator activating receptor agonists, acyl Co-A cholesterol acyl transferase inhibitors, statins, aspirin, nonsteroidal antiinflammatory drugs (NSAIDS), cyclo-oxygenase 2 (COX-2) inhibitors, and thienopyridines. Long-term treatment is advocated with drugs that achieve therapeutic levels in the brain. My own calculations of population attributable risk (PAR) suggest that hypertension might be the key target for long-term intervention to reduce the risk of VCI and possibly AD. The PAR for hypertension on VCI, for example, was about 66%.

Long-term treatment with some of these interventions in advance of the time of expected cognitive impairment may be important, as the findings from observational epidemiological studies have not been replicated in clinical trials. This has become painfully clear based on HRT trials for reduction of stroke, dementia, and heart disease. The observational epidemiological studies suggested that HRT would reduce the risk of cognitive impairment. However, a trial of estrogen plus progesterone has shown an increased risk for probable dementia, no prevention of mild cognitive impairment, and a slightly increased risk of meaningful cognitive decline with a mean follow-up time of slightly more than 4 years.

A similar disconnection has been noted for NSAIDS that were touted to reduce the risk of cognitive impairment or decline based on observational epidemiological study results that were not verified in clinical trials. In the case of NSAIDS, the linkage to AD risk is thought to be secondary to polymorphisms in inflammatory mediators such as interleukin 1α, interleukin 1β, interleukin 6, tumor necrosis factor-α, α-2 macroglobulin, and α-1 antichymotrypsin, and the reduction of β-amyloid protein production. However, post-mortem studies have suggested that chronic exposure to antiinflammatory drugs may not alleviate the amount of inflammatory glia, plaques, or tangles. In fact, low-dose steroids may not be useful in the treatment of AD. It has been suggested that NSAIDS might be more effective than steroids, as the former agents have the property of suppression of microglial activation associated with senile plaque formation.

Beyond duration of treatment, there are other reasons why HRT and NSAIDS might fail in the setting of randomized controlled trials. For example, the target disease state might be too advanced, the agent chosen could have a paradoxical or negative effect (eg, HRT and COX-2 inhibitors might be prothrombotic), and the patient characteristics of those in clinical trials might include select subjects who differ from those in the community. These and other explanations could influence the disconnection that we have witnessed between observational studies and controlled trials.

Conclusion

Vascular risk factors have measurable negative effects on the brain and our cognitive abilities. Hypertension, for example, may be associated with larger volume of brain white matter disease, smaller brain volumes, silent or strategically-placed subcortical or cortical infarcts, and loss of brain volume in structures such as the thalamus or temporal lobe.
that are important to cognition. Not only has the vascular burden of risk factors been associated with brain changes, but it has also been associated with performance decrements in multiple cognitive domains. There are a number of traditional vascular risk factors, as discussed in the above sections, to target for prevention or treatment of cognitive impairment. In addition, new avenues are opening in such areas as interventions for brain insulin receptors, statin therapy, dietary interventions, and lowering of serum homocysteine. Interventions in midlife may provide an important window of opportunity to preserve cognitive vitality later in life. We are well positioned to develop and test hypotheses in large-scale randomized controlled trials to reduce the burden of AD and VCI, the most common forms of cognitive impairment.

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