The Link Between Cardiovascular Disease and Dementia

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Introduction

Cardiovascular disease (CVD) and dementia often occur concomitantly, and much has been written about CVD as a risk factor for dementia -- with some researchers arguing that CVD can actually *cause* dementia. Others argue that CVD simply accelerates or worsens the state of dementia that has already started to develop. Study outcomes have been at variance, and the link between these coexisting disorders remains unclear.

Regardless of which disorder appears first -- the heart disease or the dementia -- or whether one is a precursor to the other, several groups of researchers have demonstrated structural changes on cerebral magnetic resonance imaging in patients with such cardiovascular risk factors as high blood pressure, high cholesterol, smoking, and diabetes.

Interest in the contributory role of homocysteine, a sulphur-containing amino acid, in the development of cognitive dysfunction, has also generated a number of studies, some of which are discussed in this column, and the potential protective effect of high-density lipoprotein cholesterol (HDL-C) on cognition has been explored.

Dementia and Stroke

Studies have reported incidence rates of dementia as high as 25% for stroke survivors, whereby the dementia was directly attributed to the stroke event.[1-4] An even stronger correlation between dementia and stroke was reported by Philip A. Wolf, MD, Boston University School of Medicine (Boston, Massachusetts), and colleagues,[5] who contended that patients who have suffered a stroke are *twice* as likely as healthy subjects to develop dementia.

Using a nested case-control study, they prospectively examined risk factors for poststroke dementia in 212 dementia-free subjects selected from the Framingham Study original cohort who had suffered a first stroke after January 1982, and compared their likelihood of developing dementia against the dementia risk of 1060 healthy, stroke-free control subjects who were matched for sex and age. The study performed a direct comparison of the risk factors for dementia between subjects who had sustained a previous stroke vs those who had not to determine whether the same factors that contribute to dementia risk in people without a previous stroke also contribute to the elevated risk of cognitive impairment in those who have suffered a stroke.

Over a 10-year follow-up period, Wolf and colleagues reported that 19.3% of stroke patients and 11% of controls developed dementia. The risk was not

reduced by adjusting the data for other possible contributing factors, such as age, sex, education level, and exposure to individual stroke factors (eg, diabetes mellitus [DM], atrial fibrillation [AF], hypertension, and smoking). It was also found that subjects with a specific genetic pattern of apolipoprotein E (apoE), a blood protein whose association with CVD has been well established, were 3 times more likely to develop dementia. Patients younger than 80 years of age and high school graduates also had a higher risk for dementia.

Unlike previous studies which have shown DM to be an independent predictor of poststroke dementia, in their analysis, Wolf and colleagues found that none of the individual risk factors they studied significantly altered the impact of stroke on the risk of dementia. Thus, they argued, independent risk factors for stroke may increase the risk of dementia simply by increasing the risk of clinical stroke.

Silent Strokes Confer an Even Higher Risk of Dementia Than Symptomatic Strokes, Study Finds

Monique M.B. Breteler, MD, and colleagues, Erasmus Medical Center (Rotterdam, The Netherlands),[6] studied the association between silent brain infarcts and the risk of dementia and cognitive decline in 1015 subjects who participated in the prospective Rotterdam Scan Study. Participants ranged in age from 60-90 years and were free of dementia (as determined by testing with the Mini-Mental State Examination [MMSE] and the Geriatric Mental State Schedule) and stroke at baseline. All subjects had undergone neuropsychological testing and cerebral magnetic resonance imaging (MRI) between 1995 and 1996, and 739 patients underwent repeat testing (including a second MRI) between 1999 and 2000. The investigators performed Cox proportional hazards and multiple linear regression analyses that were adjusted for age, sex, education level, and the presence or absence of subcortical atrophy and white-matter lesions.

By study's end (3697 person-years of follow-up), 30 patients (3%) had developed dementia and 26 of these cases were diagnosed as Alzheimer's disease (AD). Patients who had evidence of "silent" (nonsymptomatic) strokes -- ie, strokes detected radiographically as silent brain infarcts on their initial MRI scans -- faced more than double the risk of developing dementia during the study period as those who experienced strokes that were preceded by warning signs and symptoms (hazard ratio [HR], 2.26; 95% confidence interval [CI], 1.09-4.70). This remained true after adjusting for severity of white-matter lesions and subcortical atrophy. Those with silent strokes also experienced greater declines in mental function, but this finding was limited to those who had additional silent strokes during the study period that caused further damage to brain tissue.

The investigators also analyzed cognitive decline according to type of infarct and reported that silent thalamic infarcts were associated with a decline in memory performance, whereas nonthalamic infarcts were associated with a decline in psychomotor speed.

When study subjects were subclassified into 4 groups according to the presence or absence of silent brain infarcts at baseline and on follow-up MRI, the decline in cognitive function was only seen in those who had new silent brain infarcts on follow-up MRI, regardless of whether they had silent infarcts at baseline. In addition, a greater severity of periventricular white-matter lesions, believed to result from small-vessel disease, was associated with an increased risk of dementia.

Breteler and colleagues hypothesized that perhaps an infarct in a brain already affected by AD-associated abnormalities further impairs cognition, leading to clinically evident dementia. Silent brain infarcts may trigger the development of senile plaques and neurofibrillary tangles or reflect cerebral vulnerability or a certain vascular risk profile that enhances AD-associated abnormalities.

They concluded that the presence of silent brain infarcts on MRI identifies persons at increased risk for dementia, probably because these patients continue to have additional brain infarcts, both silent and symptomatic, that decrease their cognitive function.

Is CVD a Precursor to AD?
Although CVD has been hypothesized by some investigators to be a precursor to AD, there are others who believe that stroke may represent an independent injury that simply worsens the symptoms of AD whose development is already under way.[7]

Seeking to clarify the association between stroke and AD, Lawrence S. Honig, MD, Gertrude H. Sergievsky Center (New York, NY), and colleagues[7] studied a cohort of Medicare recipients from 3 ethnic groups in upper Manhattan, New York City who did not have dementia at baseline. In this longitudinal follow-up study conducted from 1992 through 1999, the investigators calculated incidence rates for AD among those with and without stroke and performed medical evaluations and neuropsychological testing.

Of the 1766 study participants, 331 (19%) suffered stroke during the study, 188 of whom had a history of stroke at baseline. An additional 143 patients developed stroke during follow-up and before the onset of dementia. Dementia was diagnosed in 212 (12%), and Alzheimer's disease was diagnosed in 181 (85%) of those 212 patients by study's end.

The authors reported that the annual incidence of AD was 5.2% per person-year among individuals with stroke and 4% per person-year for those without stroke. The hazard ratio for AD in the stroke patients was 1.6 (95% CI, 1.0-2.4; P = .04) compared with the group without stroke. In addition, patients with stroke had earlier onset of AD than those without stroke (onset at 85.3 vs 88.7 years of age, respectively).

Honig and colleagues also examined the independent influence of other cardiovascular risk factors on the incidence of AD, stratifying the analyses by each factor: hypertension, type 2 DM, and heart disease. Of these risk factors, only diabetes was an independent risk factor for AD in the absence of stroke.

Stroke remained weakly associated with AD in the absence of these independent variables, but the risk of AD was significantly increased when stroke was accompanied by the additional factors of hypertension (relative risk [RR], 2.3; 95% CI, 1.4-3.6), diabetes (RR, 4.6; 95% CI, 2.2-9.5), or heart disease (RR, 2.0; 95% CI, 1.2-3.2). Any combination of these 3 risk factors, when added to stroke, led to a significantly increased risk of AD.

Investigators also found that persons with stroke showed an earlier onset of AD as compared to those without stroke. Stroke in the absence of these risk factors remained weakly associated with AD, but did not achieve statistical significance. Thus, the investigators concluded that the association between stroke and AD was highest in those groups who had at least 1 vascular risk factor concomitantly with stroke. Of all 4 vascular variables analyzed independently (stroke, hypertension, diabetes, and heart disease), only stroke by itself was statistically significantly related to dementia.

The researchers admitted that a limitation of their study is the possibility that, despite the neurologic and neuropsychological data suggesting the diagnosis of AD, the primary neuropathologic abnormalities present in these patients may have actually been those of vascular dementia, not AD, in some cases.

"The presence of neuropathologic changes in AD could predispose some individuals to stroke, perhaps owing to amyloid angiopathy, brain parenchymal changes, or the secondary consequences of the presymptomatic disease (eg, dietary or activity changes)," the study authors wrote. "Whether stroke is directly involved in the pathogenesis of AD or acts indirectly as a contributor to the manifestations of AD needs to be established." The authors believed that stroke prevention and risk factor management "may have important implications for AD risk and deserve further investigation."

Risk for Both AD-Associated and Vascular Dementia Higher in Patients With CVD

Anne Newman, MD, University of Pittsburgh School of Medicine (Pittsburgh, Pennsylvania), and colleagues[8] conducted an analysis of patients from the Cardiovascular Health Study and found that individuals with CVD have a 30% higher risk of developing both Alzheimer's-associated dementia and vascular dementia than those without CVD. They also found that the risk of dementia was highest in patients with peripheral arterial disease.

In the Cardiovascular Health Study, 5201 people aged >/= 65 years were recruited in 1989-1990 and an additional 687 blacks from 4 US communities were enrolled in 1992-1993; all subjects underwent physical and cognitive tests annually until 1999.

In their subanalysis, Newman and colleagues evaluated both traditional risk factors (eg, diabetes, hypertension, and smoking) and newly identified risk factors (eg, hemostatic factors, inflammatory markers, exposure to infectious agents, and genetic determinants) for dementia. They noted that, although the risk of AD was higher in those with CVD, the higher risk can be attributed in part to other dementia risk factors that were concurrently present in these patients.

Comorbid Conditions in Patients With AD Vary According to Race

Edward Zamrini, MD, University of Alabama at Birmingham, and colleagues,[9] conducted 2 separate analyses that compared black patients and white patients with probable AD to determine whether the black subjects were more predisposed to certain medical comorbidities than a similar cohort of white patients and vice versa.

In the first analysis, 166 black patients (41 men and 125 women) and 166 white patients (41 men and 125 women) were matched according to their compatibility on 4 variables thought to be important in influencing other medical illnesses: age at presentation to the clinic, age at AD onset, duration of illness, and Mini-Mental State Examination (MMSE) scores. In the second analysis, investigators randomly chose 167 white probable AD patients for comparison against the 167 previously selected black patients with probable AD.

Whether groups were deliberately matched or randomly matched, the outcome was the same: blacks with probable AD had a greater frequency of hypertension, without associated CVD or heart disease, than white patients with probable AD (34% of black men and 29% of black women vs 17% of white men and 20% of white women; $P < .025$), whereas white AD patients had a greater frequency of AF ($P < .001$) and cancer ($P < .025$) than black AD patients. Because these observations were made in both analyses, the authors concluded that there are race variations among patients at least with regard to the 3 comorbid medical illnesses occurring in the studied patient population. However, the authors admit that their Memory Disorders Clinic patients may not be representative of the patients residing in the general community.

Early Signs of Cognitive Deterioration in Patients With Cardiovascular Risk Factors

A small study conducted by Ian Cook, MD and colleagues,[10] from the University of California at Los Angeles, found that the progression of certain structural changes in the brain was more pronounced among subjects with cardiovascular risk factors such as high blood pressure, high cholesterol, smoking, and diabetes.

The researchers administered a series of tests, including MRI testing, to a cohort of 29 healthy adults aged >/= 60 years to evaluate their mental function at the study's outset and then again 2 to 6 years later. MRI evaluation assessed 2 types of brain structure changes: atrophy (shrinkage) and white matter hyperintensities.

Compared with baseline MRI, on the second MRI scan, most patients showed a progression in brain atrophy and white matter lesions, and those with cardiovascular risk factors showed greater white matter changes than those without risk factors did. Despite the changes in MRI, there was little change in any of the patients' performance on the mental tests from baseline to follow-up.

The investigators noted that these structural changes in the brain can arise from mini-strokes, but healthy older people may also show similar structural changes, to a lesser degree. Cook and his colleagues term these subtle early signs of

disease "subclinical structural brain disease" (SSBD). Past research has tied greater degrees of SSBD to poorer mental functioning, they noted. Therefore, "the same measures for preventing heart attack and stroke – exercise, healthy diet, medications for conditions such as high blood pressure – might also guard against "more subtle changes" in mental function," they concluded.

Hypertension and Dementia

High blood pressure may cause changes in blood flow and brain activity that affect short-term memory, according to a study by J. Richard Jennings, MD, University of Pittsburgh and Western Psychiatric Institute (Pittsburgh, Pennsylvania).[11] Using brain imaging techniques, Dr. Jennings compared blood flow in the brains of 33 patients with hypertension and 62 patients with normal blood pressure. Patients ranged in age from 50 to 70 years; all subjects underwent ultrasound and MRI scans of their carotid arteries, positron emission tomography (while asked a number of standard memory tests), and a series of neurologic and psychological function tests. The hypertensive patients were not taking medication and had no history of stroke. Overall, the patients with high blood pressure scored slightly worse on tests of short-term memory, and those with measurable working memory impairment had less blood flow in the prefrontal and parietal regions of the brain than the patients with normal blood pressure.

Impact of Diabetes on Dementia

The frequently reported association between DM and impaired cognitive function suggests that DM may contribute to AD. However, few prospective studies have examined the relationship between DM and incident AD, and those that have focused on this association have yielded inconsistent results.

Zoe Arvanitakis, MD,Rush Alzheimer's Disease Center (Chicago, Illinois), and colleagues[12] analyzed data from the Religious Orders Study, an ongoing longitudinal study of aging and AD in Catholic nuns, priests, and brothers aged >/= 55 years, to test the hypothesis that DM was associated with an increased risk of AD and with more rapid cognitive decline. For a mean of 5.5 years, 824 subjects underwent annual evaluations that included clinical classification of AD and detailed testing of cognitive function. Follow-up was conducted for up to 9 years. Of the 824 participants, 132 (16%) experienced 1 or more strokes (at the baseline or follow-up evaluation). The association of DM with AD was not substantially changed after adjusting for stroke (HR, 1.58; 95% CI, 1.05-2.38). In a subsequent model, the researchers found no evidence for an interaction between DM and stroke (P = .68).

Although an association between DM and the pathologic features of AD has not been established, investigators point out that recent data raise the possibility of a more direct relationship between DM and AD. For example, insulin has been reported to be related to memory function in patients with AD and to plasma amyloid level and other studies have suggested potential genetic and cell-based relationships between insulin and AD.

Cognitive Decline in DM Patients in the Nurses' Health Study

A report from The Nurses' Health Study[13] also supports the correlation between cognitive decline and diabetes. This ongoing prospective study of a cohort of more than 120,000 female registered nurses in the United States was designed to examine the association between DM and poor cognitive performance or cognitive decline over 2 years of follow-up. Extensive information on DM and numerous covariates has been collected and reported via mailed questionnaires administered biennially since 1976.

From 1995 to 2001, Giancarlo Logroscino, MD, and colleagues,[13] Harvard School of Public Health (Boston, Massachusetts), administered baseline telephone cognitive interviews to 18,999 women, aged 70 to 81 years who had not had a stroke and did not have type 1 diabetes, gestational diabetes, or unconfirmed diabetes; 2-year follow-up interviews have been completed in 90% of the participants. Global scores were calculated by averaging the results of all tests (telephone interview of cognitive status, verbal fluency, immediate and delayed recalls of the East Boston memory test, delayed recall of 10-word list, and digit span backwards).

The investigators identified women who reported that they had been diagnosed with diabetes before the baseline cognitive interview. At baseline interview, 1394 women (7.3%) had type 2 diabetes, with a mean duration of 12 years since diagnosis. The diabetic women had higher incidences of hypertension, high cholesterol, heart disease, obesity, and depression than the women without diabetes. On every cognitive test, mean baseline scores were lower for women with diabetes. After adjusting for potential confounding factors, the investigators found that women with diabetes were at 25% to 35% increased odds of having a poor baseline score on the Telephone Interview of Cognitive Status (TICS) and the global composite score compared with nondiabetic women. With longer duration of diabetes, there was a 50% elevation of odds of poor baseline performance. Patients who reported metabolic complications (ketoacidosis, coma) had a higher risk of poor performance compared with nondiabetic subjects. These findings all held true when the researchers examined cognitive decline over time (for example, on the TICS, the risk of substantial cognitive decline was 26% higher for women with DM compared to those without, and this number rose to a 64% elevation with long duration of diabetes).

The investigators concluded that women with type 2 diabetes appear at increased odds of poor cognitive performance and substantial decline over a period of 2 years and that the increase in risk is especially high for subjects who have diabetes of longer duration, report metabolic complications, and do not take antidiabetic medications.

Metabolic Syndrome and its Effect on Stroke Outcomes

Recently reported by P Verhaegen, MD, and colleagues,[14] Syracuse University (Syracuse, New York), The Berlin Aging Study was designed to assess the relationship between cognitive functioning (perceptual speed, memory, fluency, and knowledge) and cardiovascular and metabolic disease in a sample of elderly adults (aged </= 70 years), both cross-sectionally (n = 516) and

longitudinally (n = 206), with a 4-year follow-up. After controlling for certain variables (age, socioeconomic status, sex, and dementia status), the following 4 diagnoses were negatively associated with cognition: (1) congestive heart failure, (2) stroke, (3) coronary heart disease, and (4) DM. Perceptual speed and fluency were the cognitive factors most severely curtailed by disease status; memory was affected only by the presence of diabetes; and knowledge was not affected by any of the disorders studied. The authors reported that the only cardiovascular risk factor associated with cognitive performance in this study was alcohol consumption.

High Homocysteine Levels Contribute to Cognitive Dysfunction

Interest in homocysteine as a risk factor for CVD has mounted during the last few years. It has been suggested that high levels of this sulphur-containing amino acid can elevate the risk of dementia and depression and can confer significant morbidity and mortality. With the advent of simple assays, homocysteine measurement has become accepted as a standard and routine clinical test.[15]

During the past 15 years, it has been thoroughly documented that moderate elevation of homocysteine levels in serum or plasma is a strong and independent risk factor for occlusive arterial disease and venous thrombosis, and is a predictor of vascular and all-cause mortality. As many as 50% of patients with stroke and other atherothrombotic diseases have high homocysteine levels (> 15 micromol/L).[15]

An association between elevated homocysteine levels and impaired cognitive performance and dementia has also been documented. Several prospective studies have demonstrated that folate and/or vitamin B_{12} status and elevated levels of homocysteine are predisposing factors for the development of dementia or contribute to an accelerated rate of progression of the disease.[15]

Reduction of homocysteine levels has been shown to increase regional cerebral blood flow and to have a positive impact on cognitive performance in elderly individuals with mild cognitive impairment. However, early intervention appears to be crucial, because severe underlying neuronal and vascular damage is irreversible (although studies in animals suggest the possibility of reversibility of neuronal damage). Vitamin therapy has also been demonstrated to influence the rate of progression of atherosclerosis and to increase endothelium-dependent blood flow.[15]

Does Levodopa Increase Heart Disease Risk by Raising Homocysteine Levels?

Dr. Ramon Diaz-Arrastia, from University of Texas Southwestern Medical Center (Dallas, Texas), and colleagues[16] measured homocysteine levels in blood samples obtained from 235 Parkinson's disease (PD) patients, including 201 patients who had been treated with levodopa. They observed a statistically modest increased risk of heart disease in PD patients with elevated homocysteine. Furthermore, levodopa users in their study showed significantly higher blood levels of homocysteine than PD patients who had not taken the drug.

The investigators considered the possibility that low levels of vitamin B_{12} and folic acid, which are common causes of elevated homocysteine levels in the blood, had contributed to the increased risk of heart disease, but deficiencies of these vitamins did not explain the elevated homocysteine levels among patients who had used levodopa in their study. However, they noted that the retrospective nature of the study made it impossible to conclude definitively whether levodopa therapy was responsible for the increased prevalence of vascular disease. Nevertheless, they do recommend that patients being treated with levodopa should ask their neurologists to monitor the level of homocysteine in their blood, particularly if they are at risk for heart disease.

The authors added that further exploration of this issue is warranted, in light of the fact that approximately one third of PD patients develop dementia during the course of their disease, and therefore it would be important to establish whether levodopa is partly responsible for increasing that risk.

Plasma Homocysteine Levels: PD Patients vs AD Patients

Diaz-Arrastia, MD, and colleagues[17] also conducted another study that compared plasma homocysteine levels in PD patients to those in AD patients in a prospectively characterized outpatient clinic population. They hypothesized that the differences between AD patients and controls with regard to homocysteine levels reported in prior studies may have become less pronounced because of the recent supplementation of folate in the food supply and widespread use of multivitamins. The results of their study indicate that plasma homocysteine levels increased with age and with carbidopa/levodopa use.

Between February 2001 and June 2002, the researchers obtained plasma samples from patients in the Memory and Movement Disorders Units of Massachusetts General Hospital with a diagnosis of AD (n = 145), mild cognitive impairment (MCI; n = 47), PD (n = 93), and no dementia (n = 88). They also collected data on age, sex, race, education, family history of AD/dementia, diagnosis, disease duration, disease severity, and medication use (eg, use of cholinesterase inhibitors, estrogen, carbidopa/levodopa use, dopamine agonists, anti-inflammatory agents, antioxidants, statins, and multivitamins). Results demonstrated that homocysteine levels were increased in the PD patients compared with AD patients, those with MCI, and dementia-free control subjects. The elevated levels within the PD group were primarily seen in PD cases taking carbidopa/levodopa. Age was associated with increasing homocysteine levels in all 3 groups. Analysis of the cohort as a whole demonstrated that individuals taking multivitamins had lower homocysteine levels compared with those not taking multivitamins.

High Levels of HDL Cholesterol Not Only Reduce the Risk of Heart Disease, But Also May Preserve Cognitive Function

The fact that high levels of HDL-C confer a protective benefit in preventing heart disease is undisputed, but limited data have been reported examining the effects of HDL-C on cognitive function.

Nir Barzilai, MD, and colleagues,[18] Albert Einstein College of Medicine (New York, NY), evaluated HDL levels and mental function in a group of very elderly patients (N = 139; age range, 95 to 107 years). They found that blood levels of HDL correlated significantly with mental function, as measured by the MMSE. Each decrease in plasma HDL tertile was associated with a significant decrease in MMSE score. Furthermore, increased plasma apoliprotein A-I levels and decreased plasma triglyceride levels were associated with significantly superior cognitive function. The investigators concluded that HDL-C may have protective effects on cognition by contributing to the proper functioning of blood vessels and by reducing inflammation.

Conclusion

As evidenced by the aforementioned studies, as well as many others not described here, the relationship between CVD and dementia continues to be a topic of much interest. A complex and intricate relationship exists between heart disease and dementia that warrants continued research, including practical applications to diagnose and treat the concomitant conditions in clinical practice. Dementia will become a growing burden to society as life expectancy increases, so the time to seek clarification of the relationship between heart disease and dementia is now.

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