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Scientific Update™

Getting to the Heart of Alzheimer's Disease: The Link Between Vascular Risk Factors, Cardiovascular Disease, and Alzheimer's Dementia

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Dementia is a topic of great importance to physicians involved in the care of patients with cardiovascular disease (CVD). Up to 10% of persons aged >65 years may develop the most common form of dementia, Alzheimer's disease (AD). AD is a progressive neurodegenerative disorder characterized by the presence of a specific distribution of plaques and tangles in the brain. This undermines the concept, held in the past, that dementia was just a normal part of aging, although it is, of course, aging-associated. Many risk factors for CVD are also risk factors for dementia. In fact, patients with vascular risk factors and CVD have a substantially increased risk of developing dementia. For instance, a cardiovascular patient aged >75 years has an approximate 50% risk of developing some degree of dementia. There has been a significant shift in the thinking about the spectrum of dementia. While previously, the neurodegenerative dementias, such as AD, were considered to be quite separate from the vascular dementias ("multi-infarct dementias"), it is currently recognized that vascular disease is linked to AD and that there are also mixed conditions, in which vascular disease and neurodegenerative changes overlap. This issue of *Cardiology Scientific Update* explores the links between vascular risk factors, CVD, and AD, and emphasizes the importance of recognizing that cognitive impairment and dementia are extremely common in the cardiovascular patient.

Contrary to the separation between the vascular and neurodegenerative dementias in the past, recent evidence suggests that AD may be initiated by vascular factors that precede neurodegenerative changes. Vascular risk factors now recognized to be associated with AD are hypertension, hypercholesterolemia, diabetes mellitus, obesity, the apoE ε4 allele, as well as the presence of CVD.[1] The best evidence linking AD and CVD involves arterial hypertension. The Honolulu-Asia Aging Study, a 26-year longitudinal analysis of >3700 Japanese-American men, demonstrated that the risk of poor cognitive function and AD in later life was progressively greater with increasing levels of blood pressure during mid-life.[2] The Kuopio study from Finland showed a similar correlation with systolic blood pressure (Figure 1).[3] These 2 studies are cited as examples, but several others have shown similar findings.[4,5] Additionally, at autopsy, patients with increased mid-life blood pressure had greater brain atrophy and greater numbers of neuritic plaques and neurofibrillary tangles, the neuropathological hallmarks of AD.[6]

Interestingly, the early predictive value of hypertension continues into older age, as demonstrated in the results of a longitudinal study, which revealed that increased blood pressure at age 70 positively correlates with the development of AD between 9 and 15 years later.[4] However, blood pressure actually decreased after the onset of AD, illustrating the importance of conducting long-term longitudinal analyses to establish the true association between hypertension and AD and suggesting that lower blood pressure may, in fact, be a consequence of AD.[7,8]

There is also evidence from many studies that lowering blood pressure with anti-hypertensive medications decreases the risk of AD and dementia by 24%-38%, whereas there are no studies showing that treatment of hypertension increases the risk of AD.[9-11] Similar data exist for the association between AD and increased lipid levels. Longitudinal studies have shown that mid-life hypercholesterolemia may also

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Figure 1: Raised mid-life BP increases the risk of Alzheimer's disease in later life[2,3]

Honolulu-Asia Aging Study n = 3703 Mean age at Baseline = 52.7 years Follow-up = 26 years		Kuopio Study, Finland n = 1409 Mean age at Baseline = 50.4 years Follow-up = 21 years	
Diastolic BP	**OR for AD (95% CI)**	**Systolic BP**	**OR for AD (95% CI)**
Normal (80-89 mm Hg)	1.0	Normal (< 140 mm Hg)	1.0
High (≥ 95 mm Hg)	4.47 (1.53-13.09)	High (≥ 160 mm Hg)	2.8 (1.1-7.2)

increase the risk of cognitive decline later in life. In a population-based study of Finnish men, the current presence of AD was significantly associated with high cholesterol levels 15-30 years earlier.[12] Furthermore, a more recent study, in an elderly mixed-sex population aged approximately 50 years at baseline, demonstrated that individuals with high baseline cholesterol levels were more likely to develop AD after a mean follow-up period of 21 years. In fact, the risk in individuals with higher cholesterol levels was more than twice that of their counterparts with "average" levels.[3] Additionally, the investigators also found a dose-response relationship between elevated blood pressure and cholesterol levels at mid-life and the severity of cognitive decline in later life (Figure 2).[13] It has been suggested that treatment of hypercholesterolemia with statins may have a modest role in decreasing the risk of dementia.[14]

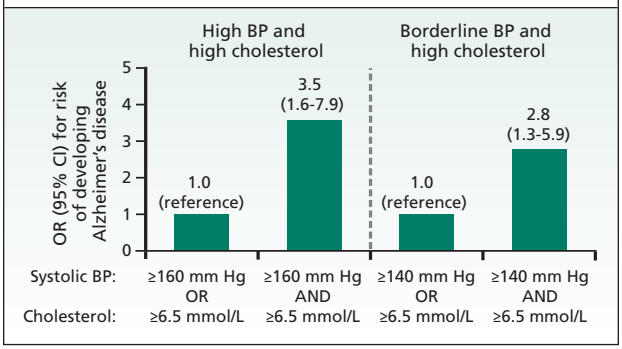
There is also a significant association between diabetes mellitus and AD. Previously, studies examining this association focused on elderly patients. More recently, however, a study in diabetic patients aged 47-57 years showed that there was a significant association with cognitive decline 6 years later.[15] These findings suggest that diabetes in mid-life may also influence the development of AD later in life. Obesity has also been identified as a risk factor for AD, with increasing risk in relation to increasing body mass index.[16]

The presence of CVD also has an impact on the risk of developing AD. Atherosclerosis, atrial fibrillation, peripheral arterial disease, and heart failure are associated with an increased risk of AD.[17,18] The Rotterdam study, using an atherosclerosis score, found that higher scores were associated with progressively higher risks of AD and that individuals in the highest score group exhibited a 3-fold increase in the risk of AD.[19] A recent study also found an association between peripheral arterial disease and the risk of AD. In fact, there was an inverse correlation between the ankle-brachial index and the risk of AD.[18]

A recent small study reported an association between the presence of heart failure and the risk of developing AD.[20] The Rotterdam study also reported that atrial fibrillation was associated with a nearly 3-fold increase in the risk of AD.[21]

Recent evidence also suggests that the presence of multiple risk factors has a cumulative effect on the risk of AD.

Figure 2: Mid-life hypertension and hyperlipidemia: Cumulative risk factors for Alzheimer's disease in later life[3]



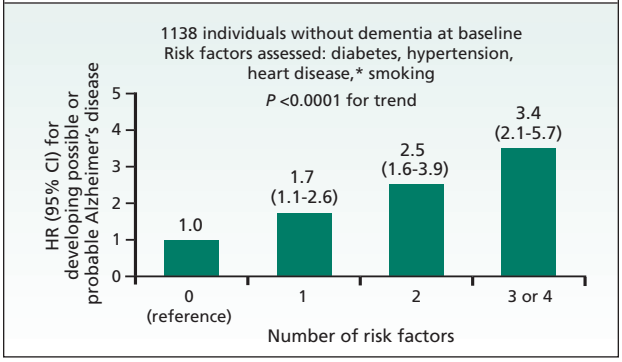
Elderly patients with a combination of 3 or 4 vascular risk factors (including diabetes, hypertension, heart disease, and current smoking) had a higher risk of AD than patients with only 1 or 2 risk factors. In turn, the latter had a higher risk than patients with no risk factors (Figure 3).[22] Similar findings were reported in a retrospective cohort analysis of >8000 individuals, aged 40 - 44 years. The risk factors analyzed in this case were smoking, hypertension, high cholesterol, and diabetes. Individuals with 3 or 4 risk factors had a greater risk of developing dementia after approximately 27 years of follow-up than those with 1 or 2 risk factors.[23]

The Alzheimer's patient: Early treatment of AD and the impact of comorbid vascular disease.

As previously discussed, many patients with CVD will also develop AD. It is, therefore, increasingly likely that physicians treating cardiovascular patients will encounter this comorbid condition and the CVD (or risk factor) and the AD will have to be treated in parallel. For this reason, it is important that physicians and other healthcare personnel who treat cardiovascular patients also learn to recognize the possible signs and symptoms of AD.

AD is a degenerative condition and its symptoms may be difficult to recognize during the earlier stages. The onset of

Figure 3: Cumulative risk factors for Alzheimer's disease[22]



*History of atrial fibrillation and other arrhythmias, MI, congestive heart failure, or angina pectoris.

dementia is gradual and cognitive decline and short-term memory impairment are typically the earliest manifestations. In the early stage of this disease, other symptoms include impaired word recall, repetition, a loss of interest in hobbies, and problems with the instrumental activities of daily living (eg, managing finances or preparing meals). With progression to the moderate and severe stages, other cognitive and functional symptoms become more prominent and there is an impaired ability to perform the basic activities of daily living (eg, washing and eating). At the advanced stage, patients also exhibit behavioural disturbances and become almost entirely dependent on caregivers.

Given that the progression of AD can be slowed with current therapeutic options, it is important to identify patients in the early stages. There are several cognitive screening tools available for this purpose, some of which are relatively easy to perform, can be used anywhere, and are not very time-consuming. It is important for physicians and healthcare personnel involved in cardiovascular care to keep in mind that AD and CVD and its risk factors commonly coexist and, in fact, as previously discussed, there is a clear association between them. It is necessary, therefore, to have an enhanced alertness for the development of the early signs and symptoms of cognitive impairment in the patient with cardiovascular risk factors or overt CVD, especially in the elderly. A review of the tools used to assess cognitive function is beyond the scope of this *Cardiology Scientific Update;* however, a couple that can be utilized with relative ease are the clock-drawing test and the Mini-Cog methodology test that includes the recall of 3 unrelated words, as well as clock-drawing.[24,25] These simple tests can be completed in 3-4 minutes and, if dementia is suspected, the patient should be referred to the appropriate specialist who will perform the necessary evaluation to confirm the diagnosis.

The treatment benefits in AD can comprise improvement, stabilization, and less-than-expected decline. The current pharmacological options available for mild to moderate AD are the cholinesterase inhibitors, such as donepezil, rivastagmine, and galantamine. The efficacy and safety of these agents have been demonstrated in several clinical trials. Unfortunately, these therapeutic options do not represent a cure and, despite short-term improvement, cognition and function decline in the long-term. Their importance is that they can slow the decline and this is, at present, quite an acceptable treatment goal for AD patients. A recent study with donepezil demonstrated that patients who received treatment after a 1-year delay following the onset of AD had a greater cognitive decline over 3 years than those who started treatment earlier in the course of the disease.[26] This finding suggests that it is crucial to start treatment as early as possible; however, the delayed donepezil treatment arm also exhibited cognitive benefits over a projected placebo group.

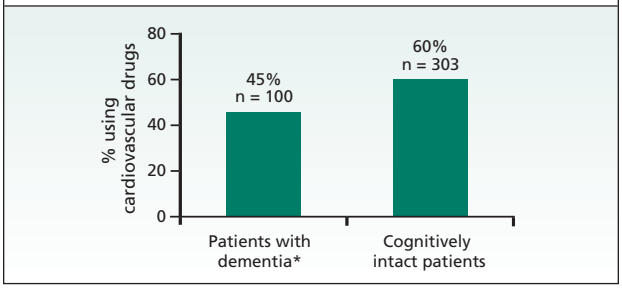
When managing patients with AD, it is also important to consider the frequent presence of comorbid conditions. As mentioned above, cardiovascular disorders are particularly frequent in these patients. This point was illustrated by a recent report in >14,000 patients enrolled in a Medicare, managed-care, organization in the United States. Of 1,366 patients with AD, approximately 25% had also been diagnosed with congestive heart failure and 10% had suffered a myocardial infarction.[27] Furthermore, CVD is associated with higher healthcare costs and a higher mortality rate in AD patients than in non-AD patients,[28] emphasizing the importance of a global approach that ensures the appropriate treatment of the AD, as well as coexistent cardiovascular risk factors or conditions.

The role of the physician in the early recognition of cognitive decline

As previously discussed, current evidence indicates that individuals with uncontrolled hypertension, hypercholesterolemia, diabetes, or atherosclerotic disease are at a markedly increased risk of developing AD. It is very likely, therefore, that cardiologists and the other physicians caring for cardiovascular patients will play increasingly important roles in identifying and referring patients with early signs and symptoms of AD. This is a progressive and degenerative disease and, often, the early manifestations are confused with "normal aging." The early indications of AD generally include mild cognitive impairment such as forgetfulness and difficulty in learning new information. Early warning signs include missed medical appointments, repetitive questioning, a tendency to look at a relative or partner when asked a question, a hesitation in language or word-finding difficulty, and trouble recalling the present date. It is important to recognize these early manifestations, not only because they will make an early referral and initiation of therapy possible, but also because the impairment in patients with AD significantly hinders other aspects of cardiovascular care, such as patient communication and cooperation, adherence to medications, correct drug administration, and the ability to give informed consent for possible cardiovascular tests and procedures.

There is evidence, as well, that effective cardiovascular medications are not optimally utilized in dementia patients. One study reported that only 45% of patients with dementia in a community setting were receiving the appropriate cardiovascular medications compared with 60% of cognitively-intact patients (Figure 4).[29] Dementia is also a significant

Figure 4: Differential cardiovascular drug treatment of patients with dementia in a community setting[29]



*69 of the 100 subjects with dementia had Alzheimer's disease

independent determinant of nontreatment with aspirin or warfarin in patients with atrial fibrillation when these medications are otherwise indicated.[30] This is unfortunate since atrial fibrillation may be a modifiable risk factor in older stroke patients with dementia to reduce recurrence and death. Additionally, data from clinical trials indicate that the coprescription of cholinesterase inhibitors and many cardiovascular medications is well-tolerated. For instance, there are no significant drug interactions between donepezil and warfarin. As well, there is generally no increased risk of bradycardia when donepezil is administered with β-blockers, calcium channel blockers, or digoxin.[31] However, in view of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate. The potential for this action may be particularly important in patients with sick sinus syndrome, sinoatrial block, or atrioventricular block, and caution must be exercised in these patients. Pacemaker insertion may be indicated, rather than cessation of the cholinesterase inhibitor.[32]

Conclusion

In conclusion, patients with cardiovascular risks factors or CVD are at an increased risk of developing AD. Thus, physicians taking care of cardiovascular patients are in an excellent position to recognize those at higher risk of this condition. Simple screening tools are available that allow the rapid identification of patients who are cognitively impaired or have dementia. The administration of these screening tools would help in the detection of AD patients in the earlier stages of the disease. This is important because most AD patients with cardiovascular conditions can be treated successfully with cholinesterase inhibitors.

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