Preventing or delaying the effects of Alzheimer's disease

Alzheimer's disease seems to share the same vascular risk factors as vascular dementia and cardiovascular disease. The evidence for this, although far from complete, continues to grow, and the potential to prevent and control Alzheimer's disease should add increased urgency and enthusiasm to the control of shared risk factors. Research also suggests that the brain has considerable cognitive recuperative potential, which is maximised by control of vascular risk factors. Doctors and health-care professionals should be more active in informing and educating those at risk, from middle-age onwards, of the potential benefits of controlling these common risk factors and adoption of healthier life styles. Patients must be involved in their own health care to enable them to attain optimum health.

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Is Alzheimer's disease a vascular disorder? We do not know yet; it is probably not, or at least not exclusively vascular, but we do not have definitive evidence. It could be a result of the pathological processes of Alzheimer's disease and vascular disease contributing to the final clinical disorder. In the meantime, the profile of vascular risk factors continues to increase with regard to the causes and pathogenesis of this disease.

Age remains the main risk factor for Alzheimer's disease, and with increasing life expectancy, it becomes an ever more ominous threat. Women in developed countries have a life expectancy of 80 years. If we live to that age, one in five of us will have dementia. With current trends, by 2020 a million people in the UK will have dementia. Individually, we do not believe that we will develop this illness. We are in denial and do not wish to talk about Alzheimer's disease in a personal context. The good news is that we may be able to start talking with patients about avoidance and control of Alzheimer's disease, as we do for heart disease, stroke, vascular dementia, and cancer. We have already seen that patients respond to strategies for informing, educating, and involving them in health.[1] However, if all else fails, can we gracefully mask the symptoms of Alzheimer's disease for as long as possible? Box 1 shows the key points of this article.

It probably is not an exaggeration to state, even with the considerable limitations of current knowledge, that almost everything that increases your risk of cardiovascular disease increases your risk of not only vascular dementia, but also of Alzheimer's disease. Therefore, included in the risk factors are hypertension, hypercholesterolaemia, sedentary lifestyles, increased body-mass index, diabetes, smoking, and high blood homocystine levels (box 2). The best time to start controlling for these factors is in midlife.[2,3]

Box 1: Key points

- Vascular risk factors are assuming a larger profile in the pathogenesis and progression of Alzheimer's disease
- This knowledge gives new opportunities for research, prevention, and amelioration of heart disease, vascular dementia, and Alzheimer's disease
- Research suggests that the brain may have considerable recuperative potential, encompassing neurogenesis, angiogenesis, and synaptogenesis
- This potential may be optimised not only by controlling vascular risk factors, but also by involvement in life-long learning, intellectual challenge, and maintaining social networks
- The necessity to inform and enthuse vulnerable middle-aged individuals about the need to control these risk factors is a responsibility for doctors and health-care professionals
- If control of vascular risk factors does not prevent or delay the onset of Alzheimer's disease, then the possibility of slowing down the rate of progression may be very welcome
- If these objectives fail, then masking the illness by a change of lifestyle will be good for the morale of the patient and the carer, most frequently an elderly spouse

Box 2: Vascular risk factors that could be important in Alzheimer's disease

- Hypertension
- Smoking
- Obesity
- Poorly controlled diabetes mellitus
- High concentration of low-density-lipoprotein cholesterol
- Low concentration of high-density-lipoprotein cholesterol
- High concentrations of fibrinogen and homocysteine
- Misuse of alcohol
- Sedentary lifestyle

Other cerebrovascular risks include already established pathology such as cardiac arrhythmia, carotid atheroma, transient ischaemic attacks, ischaemic heart disease, and the metabolic syndrome

For decades we recognised the association of these factors with vascular dementia, but the connection with Alzheimer's disease is most intriguing. This linkage opens up new insights, research opportunities, and potential pathways for prevention and control, and also raises morale. Historically, Alzheimer's disease was not thought to be related to vascular dementia (which was postulated as due to cerebral arteriosclerosis), although dual pathologies were found frequently at post-mortem examination, they were viewed as separate but contributory to overall morbidity. There was also a very clear age cut-off: at 65 years and younger the patient had Alzheimer's disease (viewed exclusively as a primary degenerative brain disease, frequently referred to as presenile dementia), if older than 65 years, they had senile dementia (commonly referred to as arteriosclerotic dementia). Over time we discovered that not only did dual pathologies frequently coexist but that they also had considerable overlap in clinical progression and presentation, and that vascular pathology alone was no longer sufficient to provide a clear demarcation between the two disorders.

The evidence for a role of vascular elements in sporadic (distinct from genetic) Alzheimer's disease can be summarised broadly as follows; it is clear from epidemiological studies that nearly all risk factors for Alzheimer's disease have a vascular component leading to reduced cerebral perfusion. Parts of the brain related to memory have impaired regional cerebral blood flow in patients with Alzheimer's disease, and in those considered at risk.[4] We can now identify preclinical Alzheimer's disease with neuroimaging techniques that show regional cerebral hypoperfusion. Additionally, the presence of regional cerebral microvascular abnormalities has been noted before neurodegenerative changes and cognitive decline are detectable.[5] The overlap of clinical symptoms between Alzheimer's disease and vascular dementia has been known to clinicians for a long time, and cerebrovascular lesions are similar in most patients with Alzheimer's disease or vascular dementia. Finally, African-Americans are more likely than their white counterparts to develop Alzheimer's disease, and one suggested reason for this occurence is that they have higher levels of risk factors for vascular degeneration, particularly blood pressure and diabetes (box 3).[6]

Further support for the connection between vascular risk factors and Alzheimer's disease includes the role of cholesterol in the development of amyloid plaques. People on statins or hypotensive drugs may have a lower risk of developing dementia, and studies suggest that controlling vascular risk factors may delay or prevent the onset of this disorder.[7,8] The first physical change in the brain in Alzheimer's disease might be a decline in the amount of blood that flows to the brain. Researchers have also shown that amyloid metabolism could be related to dysregulation of cerebral blood flow—leakage occurs between the blood vessels and the brain, enhancing the development of plaques. Damaged blood vessels are also inefficient at transporting amyloid-precursor proteins away from the brain, where they accumulate and cause further damage, and enhance plaque formation. Additionally, degeneration of microvessels has been observed at terminal arterioles and capillaries in brains from patients with Alzheimer's disease compared with controls.[5] The evidence is summarised in box 3.

The relationship between vascular factors and Alzheimer's disease is only part of the story. Researchers are now reporting the presence of neural plasticity—reparative mechanisms such as synaptogenesis, neurogenesis, and cerebral angiogenesis—which is of relevance not only to young brains, but also to old and damaged brains.[10] Vascular risk factors will lead directly or indirectly to oxidative stress, which results in inflammatory cerebral events, and in turn results in vascular damage and deterioration in cognitive functioning. However, oxidative stress could lead to an increased production of vascular endothelial growth factor, which encourages angiogenesis. It is postulated that the likelihood of further damage to the brain could be prevented by controlling vascular risk factors, and that neural reparative mechanisms could be helped.

Research to identify potential causative and enhancing factors for dementia is more difficult than that for physical illness. Measurement of outcome is far more subtle and indefinite, and is confounded by a host of related psychosocial factors that are difficult to measure, standardise, and control. So far, the evidence for the effect of controlling vascular risk factors on Alzheimer's disease could be described as considerable, but definitive large scale trials are yet to be done.[11]

Box 3: Evidence for a role of vascular risk factors in Alzheimer's disease

- Preclinical Alzheimer's disease can be identified by neuroimaging techniques that show cerebral regional vascular hypoperfusion[5]
- Regional cerebrovascular abnormalities have been noted before neurodegenerative and cognitive decline in Alzheimer's disease[5]
- Degeneration of microvessels has been observed at the terminal arterioles and capillaries in brains from patients with Alzheimer's disease, compared with controls[4]
- Symptoms or progression of Alzheimer's disease can be reduced by drugs that enhance cerebral perfusion and lower cholesterol[6,7]
- All risk factors have a vascular component that results in reduced cerebral perfusion[4]
- Dual cerebral pathologies indicative of vascular disorders and Alzheimer's disease are frequently seen to coexist at post-mortem examination
- Molecular and microscopic interactions and relationships have been noted between vascular and Alzheimer's pathologies[9]
- The overlap of clinical symptoms and disease progression between Alzheimer's disease and vascular dementia has been known for decades
- The two dementias are frequently difficult to distinguish before neuroimaging
- African-Americans are more likely to develop Alzheimer's disease, which is thought to be related to the higher rates of risk factors for hypertension and diabetes in this population[6]

But we should not be deterred from controlling these factors now. The disease we try to prevent or ameliorate is so devastating, that even though the odds against success are considerable, we should enthusiastically accept this challenge. We need to involve patients and carers in this discussion.When the risk to our lungs from smoking was established most doctors stopped smoking, but were we slow or not enthusiastic and persistent in getting the message across to our patients? If doctors' efforts do not keep Alzheimer's disease away, then at least they will help patients' arteries, be conducive to better control of diabetes, and help to avoid vascular dementia, heart disease, and stroke. Indeed, improving the quality of life of patients with Alzheimer's disease by encouraging vascular health gives us nothing to lose and a huge possible gain. A poster in health centres outlining succinctly the best information we have on avoiding or controlling dementia would blend well with those for prevention of cardiovascular diseases.

An excellent review article on lowering the risk of Alzheimer's disease by Jedrziewski and colleagues,[12] weighed the evidence for risk factors other than vascular. I agree with their conclusion that although current evidence does not prove cause and effect, many of the associations have been documented in multiple community-based studies, and many interventions based on these associations have low risk and are beneficial for prevention of other diseases such as heart disease, hypertension, and diabetes.

After dealing with the negative risks we can promote cognition enhancing factors—mainly patterns of behaviour that will mobilise and sustain our cognitive reserve. A growing body of research supports the view that exercise, structured formal learning, and continued social engagement with enhancement of social networks, will result in recruitment of neural circuitry in older people, which may differ from that seen in younger people.[8] A healthy diet, and perhaps sensible vitamin supplementation, would be advisable. By changing lifestyle, with life-long learning and social engagement, patients can defend themselves against Alzheimer's disease by enhancing overall health. If these precautions do not result in either avoiding Alzheimer's disease, delaying its onset, or controlling its progression, then patients might at least mask its effects. In this era of preventive medicine, patients no longer need to passively succumb to this disease, which is good not only for the morale of the patient, but also for the carers, especially spouses who are elderly too.

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