CURRENT OPINION

CNS Drugs 2002; 16 (7): 435-444
1172-7047/02/0007-0435/$25.00/0

Hypertension and Hypercholesterolaemia as Risk Factors for Alzheimer's Disease

Potential for Pharmacological Intervention

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Abstract

This paper focuses on hypertension and hypercholesterolaemia as risk factors for Alzheimer's disease and, as such, subjects for prevention. The long-term, prospective, population-based studies regarding the relationship between hypertension or hypercholesterolaemia and Alzheimer's disease, and the clinical studies regarding the association between antihypertensive or lipid-lowering medications and the risk of Alzheimer's disease, are reviewed. These studies provide evidence to suggest that elevated blood pressure and cholesterol levels earlier in life may have an important role in the development and expression of late-life Alzheimer's disease. Based on these data, we propose that proper, early interventions aimed at reducing these cardiovascular risk factors may have an impact on the future incidence and prevalence of Alzheimer's disease.

Alzheimer's disease is the most common cause of dementia in the elderly and, as the population ages, it is becoming an enormous public health problem. It has been estimated that in the next 50 years, the prevalence of Alzheimer's disease in the US will quadruple to 8.6 million (with a range from 4.4 up to 15.4 million) patients.[1] From the same projections, it has been proposed that delaying the onset of the disease by 5 years would result in 4 million fewer cases; even delaying the onset by only 1 year would still reduce the number of patients with Alzheimer's disease by approximately 750 000.[1]

In order to determine interventions that would delay its onset, modifiable risk factors for Alzheimer's disease first have to be identified. These risk factors could then be used as targets for interventions, pharmacological or nonpharmacological. Demonstration that interventions targeted at these risk factors actually reduce the risk of Alzheimer's disease indicates a true causal relationship between a given risk factor and Alzheimer's disease.

At present, the causes, initiators and promoters underlying Alzheimer's disease are unknown. Alzheimer's disease is considered to be a disease of complex origin, resulting from interactions of multiple environmental and genetic factors. Although

genetic constitution is not modifiable, various environmental risk factors for Alzheimer's disease have been proposed, although there is no unequivocal agreement of their importance. In this paper, we focus on two proposed risk factors for Alzheimer's disease that have attracted a considerable amount of attention recently: hypertension and hypercholesterolaemia. We adopt two lines of evidence to discuss the issue. Firstly, we review the issue from the perspective of long-term, prospective, population-based studies examining the relationship between hypertension or hypercholesterolaemia earlier in life and the development of late-life Alzheimer's disease. Secondly, we review the issue from the perspective of clinicoepidemiological studies that have evaluated the association between the usage of antihypertensive or lipid-lowering medications and the risk of Alzheimer's disease.

1. Relationship between Hypertension or Hypercholesterolaemia and Alzheimer's Disease

A number of cross-sectional and short follow-up studies have investigated the relationship between blood pressure (BP) or cholesterol levels and cognitive decline or dementia, but the results from these studies have been somewhat contradictory.[2,3] These discrepancies may be explained by a number of factors, including the falls in BP[4] and cholesterol levels[5] that seem to occur before the manifestation of dementia. Furthermore, a conceptual limitation in these study settings is that they cannot prove a causal relationship, but only infer an association.

From a causal point of view, stronger evidence of the association between these vascular risk factors and Alzheimer's disease is provided by long-term, prospective, population-based studies, but until recently, such evidence has been lacking. During the last 5 years, this gap has been filled by a few studies that have follow-up times ranging from around 10 to 25 years, as described in sections 1.1 and 1.2.

1.1 Hypertension

The first long-term longitudinal study examining the relationship between BP and the subsequent development of dementia was conducted as part of the Longitudinal Population Study of 70-year-old individuals in Gothenburg, Sweden.[4] A sample of 382 individuals was followed for up to 15 years. It was found that high BP at the age of 70 years increased the risk of Alzheimer's disease 9 to 15 years later. At the time of the first examination, both systolic and diastolic BP were higher in the patients who eventually developed dementia, but the risk for subsequent Alzheimer's disease was significant for diastolic BP only.

The second study, the Honolulu-Asia Aging Study,[6] examined the association between midlife (mean age 53 years) BP with late-life Alzheimer's disease in a cohort of 3703 Japanese-American male patients followed for 25 years. It was found that elevated diastolic BP in midlife increased the risk of Alzheimer's disease. It is noteworthy that this relationship was evident only in those individuals who had never been treated with antihypertensive drugs, and there was no association between Alzheimer's disease and BP in treated hypertensive men.

The third study, our recent prospective, population-based study in Finland,[7] with an average follow-up time of 21 years in a total of 1449 individuals, found that elevated systolic BP at midlife (mean age 50 years) significantly increased the risk of late-life Alzheimer's disease. After controlling for a number of confounding factors, midlife systolic BP, but not diastolic BP, was significantly higher in the individuals who developed Alzheimer's disease. However, at the end of the follow-up, there were no differences in either systolic or diastolic BP between patients with Alzheimer's disease and patients without the disease.

In contrast to these three longitudinal studies were the results of a recent longitudinal study of 634 participants aged 65 years and older, selected as a stratified random sample of participants of the East Boston Established Populations for Epidemiologic Studies of the Elderly.[8] Morris et al.[8]

found little association between BP during 15 years of observation and risk of Alzheimer's disease. There was no evidence of increased risk of Alzheimer's disease among persons with high BP 13 years before dementia diagnosis, an inverse association for BP measured 4 years before diagnosis, and no effect of Alzheimer's disease on BP measurements 2 years after the diagnosis. In this study, however, the BP measurements for the whole follow-up period were lacking in about a third of the study population, and only a few individuals had very high BP. As suggested by the authors, this may have resulted in wider confidence intervals, which included odds ratios reported in the previous studies.[6,7]

There are no major discrepancies between the first three studies mentioned,[4,6,7] except that in the first two studies[4,6] it was diastolic rather than systolic BP that was associated with an increased risk of Alzheimer's disease. Differences in study settings and populations could account for this discrepancy. For instance, in our study,[7] the patients with Alzheimer's disease were more likely to have received antihypertensive medication at midlife, but despite treatment, they still had higher systolic BP in midlife than those who did not develop dementia. Given that increased diastolic BP has traditionally been the main indication for antihypertensive treatment, the effect of medication could account for the observed results. It is possible that, having reduced the risk of diastolic BP, the risk related with systolic BP became discernible.

From this perspective, our data should not be interpreted as minimising the potential risk of Alzheimer's disease in patients with elevated diastolic BP, but rather as emphasising the importance of elevated systolic BP as a risk factor for Alzheimer's disease, even in patients with normal diastolic BP. With aging, the systolic component of BP tends to increase, whereas diastolic BP remains the same or may even decrease, and significant health outcomes associated with BP concentrate generally on systolic BP among the elderly.[9]

In the context of prevention of Alzheimer's disease when the focus is on BP earlier in life, the diastolic versus systolic BP enigma may not be of major relevance; both elevated systolic and diastolic BP at midlife are risk factors for cerebrovascular and cardiovascular diseases, and should be treated. However, the association between different components of BP (diastolic, systolic and pulse pressure) and Alzheimer's disease needs to be further studied in different age groups and at different time points in prospective population-based studies to better understand the relationship between BP and Alzheimer's disease.

1.2 Hypercholesterolaemia

In our recent study,[7] we also found that midlife elevated cholesterol level was a significant risk factor for late-life Alzheimer's disease. Again, cholesterol levels were significantly higher during the midlife visit in the patients who developed Alzheimer's disease compared with patients who did not, but there were no longer differences in cholesterol values between the groups at the late-life visit when dementia was diagnosed. Importantly, it was also found that the combination of hypertension and hypercholesterolaemia particularly increased the risk of late-life Alzheimer's disease. Patients with both of these risk factors at midlife had a significantly higher risk for Alzheimer's disease than those with either of these risk factors alone.

The results of our study corroborate the results of an earlier study, the Finnish Cohort of the Seven Countries Study.[5] This study, conducted in 444 men, found that men aged 70 to 89 years with Alzheimer's disease had had elevated serum cholesterol levels 15 to 25 years before the onset of Alzheimer's disease. Also in this cohort, the cholesterol levels fell before the onset of Alzheimer's disease.

However, there are some prospective studies with relatively short follow-up times yielding negative or conflicting results on the association between cholesterol and Alzheimer's disease.[10-12] There is evidence that cholesterol levels gradually fall at later ages, and evidence of a more rapid decrement in those destined to develop dementia.[5,13] Thus, the temporal relationship between risk factors and Alzheimer's disease cannot be determined

unequivocally in the studies with a relatively short follow-up time. Nevertheless, these results indicate that factors associated with abnormal lipid metabolism in the development of Alzheimer's disease and in the different phases of the disease need to be further clarified in future studies.

2. Antihypertensive and Lipid-Lowering Medications and Alzheimer's Disease

In addition to the recent longitudinal studies showing a relationship between the risk of Alzheimer's disease and hypertension or hyperlipidaemia, the first studies showing a reduced incidence or prevalence of dementia in patients treated with antihypertensive drugs or lipid-reducing agents ('statins' or HMG-CoA reductase inhibitors) have recently been published.

2.1 Antihypertensive Agents

The effect of antihypertensive medication on the incidence of dementia has been studied in only a few randomised, placebo-controlled trials.

The Systolic Hypertension in the Elderly Program[14] involved 4736 patients aged 60 years and older with isolated systolic hypertension. The diuretic chlorthalidone was used as the primary drug in the active treatment group (n = 2365). After an average follow-up period of 5 years, the incidence of dementia did not differ between the active treatment (1.6%) and placebo-treated groups (1.9%).

The cognitive sub-study to the Medical Research Council trial[15] included 2584 patients with hypertension aged between 65 and 74 years randomised to a diuretic, β-blocker or placebo. No significant difference in psychometric tests was detected between the active treatment and placebo-treated groups covering a period of approximately 4.5 years.

The Systolic Hypertension in Europe (Syst-Eur) trial[16] is the first and only randomised, double-blind, placebo-controlled study to date to show that treatment of hypertension may reduce the risk of dementia and, more specifically, that of Alzheimer's disease. The study included 2418 patients aged 60 years and older with isolated systolic hypertension. Compared with placebo (n = 1180), active treatment (n = 1238) of isolated systolic hypertension with nitrendipine, a calcium channel antagonist, was found to halve the incidence of dementia from 7.7 to 3.8 cases per 1000 patient-years (21 *vs* 11 patients). The primary hypothesis of the study was that the reduction in BP would protect against vascular dementia, and thus the decrease in incidence of Alzheimer's disease was described as unexpected by the authors. The sample size in the study was large, but the follow-up time was relatively short (median of 2 years), and the number of patients with dementia quite small. The publication of this study sparked a debate on whether the effect was a result of the reduction in hypertension or the ability of calcium channel antagonists to reduce calcium-mediated neural damage; irrespective of the mechanism, the effect was present.

The ongoing extended follow-up of the Syst-Eur trial indicates that the protective effect of early active antihypertensive therapy on the risk of Alzheimer's disease persists.

The effects of antihypertensive treatment on the incidence of dementia have also been evaluated in some observational studies. In the Kungsholmen Project,[17] Stockholm, Sweden, 1301 participants aged 75 years and older without dementia at baseline were followed for an average of 3 years. Participants taking diuretics at baseline had a significantly reduced incidence of dementia. According to the authors, Alzheimer's disease accounted for more than 70% of incident dementia cases, but Alzheimer's disease and vascular dementia were not specifically differentiated in this study.

Moreover, the association of antihypertensive drug use and the risk of dementia was recently investigated in the Rotterdam Study.[18] This observational study of 7046 elderly individuals aged 55 years or older, free of dementia at baseline, reported that after a mean follow-up time of 2.2 years, antihypertensive medication protected patients from vascular dementia, but no significant protective effect was found for Alzheimer's disease. The authors concluded that although dementia may be prevented by antihypertensive treatment

in patients with hypertension, larger studies with longer follow-up periods are needed to confirm the relationship between BP changes and the risk of Alzheimer's disease.

2.2 Lipid-Lowering Agents

Two recent retrospective clinical studies have reported significantly reduced rates of dementia in patients who had used statins as cholesterol-reducing drugs. A cross-sectional analysis, including 57 104 patients aged 60 years and older from databases at three different hospitals, reported a 60 to 73% reduced prevalence of Alzheimer's disease in the cohort taking statins compared with the total population.[19] The protective effects were found for lovastatin and pravastatin, but not for simvastatin or other medications typically used in the treatment of hypertension and cardiovascular disease. One potential reason for the negative association for simvastatin may lie in differences in physician prescribing patterns; simvastatin is a slightly newer drug than the two other statins, and the authors later reported that prescription of simvastatin in their institute had begun more recently than the other two statins.[20]

Another study derived data from the General Practice Research Database in the UK, consisting of a base population of 60 901 individuals aged 50 years and older. From these data, Jick et al.[21] used a nested case-control study design with 284 patients with dementia and 1080 control individuals. The study did not distinguish between Alzheimer's disease and other forms of dementia. The risk of dementia was found to be up to 70% lower in individuals using statins than in those who did not have hyperlipidaemia or in those with untreated hyperlipidaemia. It is noteworthy that individuals with hyperlipidaemia receiving lipid-lowering drugs other than statins did not have a reduced risk of dementia. The protective effect was similar for all individual statins, including simvastatin.

Although these results suggest a protective effect of statins on dementia, they are also subject to some limitations. The study designs used are susceptible to indication bias, and information on important potential confounding factors, such as education, were not available. However, a recent secondary analysis[22] of the Canadian Study of Health and Aging, a population-based survey of Canadians 65 years and older, examined the issue using a cohort design (n = 2305) to assess the possibility of indication bias and a case-control setting to evaluate whether the use of lipid-lowering agents was associated with a reduction in dementia (492 patients with incident dementia and 823 control individuals). To minimise indication bias, only incident dementia cases were studied (mean follow-up 4 to 5 years). No indication bias was found, and the use of statins and other lipid-lowering agents was associated with a lower risk of dementia and specifically of Alzheimer's disease in individuals younger than 80 years even after adjustment for gender, education and self-rated health. Thus, this study supports the observation of a protective association between statins and dementia and suggests that it might also be extended to other lipid-lowering agents.

3. Future Perspectives

3.1 Antihypertensive Medications and Statins

In summary, some prospective epidemiological studies have reported that elevated BP and cholesterol are risk factors for late-life Alzheimer's disease.[4-7] In addition, a few studies have reported a reduced incidence or prevalence of Alzheimer's disease in patients treated with antihypertensive agents or statins.[16,17,19,21,22] Together, these data suggest that there may be a causal relationship between these proposed risk factors and Alzheimer's disease. However, some studies with antihypertensive agents have reported only modest or no protective effects on Alzheimer's disease.[14,18] This variation in results from these latter studies can be attributed to problems in study design, sample size or the duration of the follow-up. It must be noted that to date no trial has been designed specifically to assess the prevention of Alzheimer's disease in

patients with hypertension, and the above results have been derived from secondary analyses only.

One plausible reason for the modest effect that lowering BP has on later development of Alzheimer's disease or dementia in some observational studies may be that a considerable proportion of patients receiving treatment for elevated BP do not achieve the targeted BP levels. Studies on treatment of hypertension in Finland suggest that target levels are achieved in only about 20 to 40% of patients with hypertension,[23,24] and similar figures have been reported throughout the world.[25] Diagnosis of hypertension or hypercholesterolaemia and prescription of drugs to treat these conditions does not assure that the compliance with or efficacy of the treatment is adequate.

The issue of various antihypertensive agents and their putative beneficial and deleterious effects on cognitive function has been reviewed by Wyss and van Groen.[26] They concluded that none of the antihypertensive drugs in use at the time had been demonstrated to have a major deleterious effect on cognition in patients with hypertension, but some of the drugs may have more beneficial effects on cognitive function. Angiotensin-converting enzyme inhibitors as a class of antihypertensive drugs were proposed most consistently to lead to cognitive improvement; in addition, β-blockers and a subset of calcium channel antagonists appear to have very similar effects.

Comparative studies between different drug categories have not been done, nor are such trials underway. Performing a formal randomised clinical trial is the gold standard to establish treatment effects. However, to specifically study this issue prospectively today would be problematic; it is no longer considered ethical to study the prevention of Alzheimer's disease in randomised, placebo-controlled trials, and not to treat hypertension and/or hypercholesterolaemia. Instead, perhaps mining data from previous drug trials might provide material suitable for studying the current prevalence or incidence of Alzheimer's disease in a given study population. Another possibility is to initiate new randomised trials comparing the specific effects of the various antihypertensive and lipid-lowering drug classes on cognitive function and the occurrence of Alzheimer's disease.

Another issue to be considered is that it may be *early* interventions that reduce the risk of Alzheimer's disease. Pathological studies have shown signs of Alzheimer's disease neuropathology relatively early in midlife, suggesting that the pathological cascades leading to Alzheimer's disease may have already started by that time.[27] Late interventions, at the onset of cognitive impairment, may simply be too late. Reducing BP vigorously in patients who already have dementia may have detrimental effects on cerebral blood flow, and may thus only worsen cognitive function. Antihypertensive medications appear to have no negative effects on cognition in general, but there are differences in adverse effects (which may affect cognition), and some drugs have been associated with deficits in some aspects of cognitive functions. These deficits may be more prominent in older patients.[26]

In addition, the use of statins may result in a decline in some cognitive functions, but whether this has any clinical significance is uncertain.[28,29] In many studies, treatment with statins has not been found to substantially alter cognitive functions.[30-33] Still, even though hyperlipidaemia may be a risk factor for Alzheimer's disease, once Alzheimer's disease has developed the brain may in fact be lacking in cholesterol as a result of defects in cholesterol metabolism and/or bioavailability of cholesterol.[34] At present, there are no data available on whether patients with manifest Alzheimer's disease would benefit from statin treatment. Although there is a theoretical background suggesting putative beneficial effects of statins, particularly in terms of slowing the progression of Alzheimer's disease,[35] there is also a possibility that statins might have detrimental effects on cognition in patients with Alzheimer's disease if their brains lack cholesterol. The real effects must therefore be determined in prospective, controlled trials.

3.2 Possible Mechanisms

At present, the precise pathophysiological mechanisms to explain why elevated BP and cholesterol levels increase the risk of Alzheimer's disease are not known. Thus, the modification of these factors without first pinpointing the critical aetiological pathways may not be optimally effective. Hypertension and hypercholesterolaemia have been suggested to increase the risk of dementia, for instance by inducing atherosclerosis and impairing blood flow, but they may also directly induce Alzheimer's disease neuropathology.[36]

Hypertension is a risk factor for white matter lesions and cerebral infarcts, both of which are commonly found in elderly patients with dementia. As a result of the summation of the various types of lesions, stroke, even though it has only minor physical manifestations, may lead to an increased progression towards cognitive decline in patients with Alzheimer's disease.[37] The Nun study[38] reported that fewer neuropathological lesions of Alzheimer's disease resulted in dementia in those patients with lacuna infarcts. There is also evidence of a direct association between hypertension and the neuropathological markers of Alzheimer's disease and brain atrophy.[39,40]

There are many neurobiological theories to explain why elevated cholesterol levels could lead to the development of Alzheimer's disease. Longstanding hypercholesterolaemia may lead to intima thickening and weakening of endothelial functions in cerebrovascular arterioles and capillaries, and these changes may have disastrous effects on brain metabolism.[41] Cholesterol may also modulate amyloid precursor protein (APP) metabolism. Interesting experimental studies examining ways that cholesterol lowering might influence Alzheimer's disease and APP metabolism,[42,43] further discussions on the issue[44,45] and a review on the relationship between cholesterol and the amyloid hypothesis[35] have been published recently. Depletion of intraneuronal cholesterol has been reported to inhibit β-amyloid production *in vitro*[46] and *in vivo*.[42] It has also been reported that the actual plaque formation can be inhibited and that the observed effects are not drug-specific; the cholesterol synthesis inhibitor BM15.766 has been reported to reduce plaque formation in transgenic mice.[47] In addition, it has been observed that inhibition of APP β-secretase occurs in parallel to cholesterol reduction;[46] in contrast, the activity of the α-secretase is increased upon cholesterol reduction.[43] Thus, cholesterol reduction appears to modulate the major APP secretases in such a way that they switch from the amyloidogenic to the non-amyloidogenic pathway.[48]

It should also be noted that blood cholesterol and brain cholesterol levels are in two separate pools, and, therefore, studies measuring serum cholesterol level observe only the tip of the iceberg.[48] The recent studies showing reduced rates of Alzheimer's disease in patients taking statins[19,21,22] do not indicate whether this is a result of a reduction in plasma cholesterol levels, decreased cholesterol synthesis in the CNS or other mechanisms.

In addition to reducing cholesterol levels, statins appear to have a variety of mechanisms of action that may be beneficial for the CNS and be associated with a reduced risk of Alzheimer's disease, including endothelial protection via actions on the nitric oxide synthase system, and antioxidant, anti-inflammatory, antiplatelet and immunomodulatory effects.[49,50] Interestingly, a recent study[51] showed for the first time that simvastatin modifies cholesterol metabolism in the human brain and reduces the level of plasma 24S-hydroxycholesterol, which is synthesised in the CNS. Furthermore, the percentage of reduction occurred independently of the reduction in total cholesterol, indicating that simvastatin reduces cholesterol turnover in the human brain.

3.3 Diagnostic Aspects

It should be noted that, like most of the studies on Alzheimer's disease, the studies outlined in sections 1.1, 1.2, 2.1 and 2.2 have been criticised for their lack of pathological confirmation. Clinical diagnosis of Alzheimer's disease may have introduced some bias towards the diagnosis of degen-

erative dementias, since some forms of dementia (e.g. subcortical vascular dementia) that are difficult to distinguish from Alzheimer's disease on clinical grounds may have been included in the Alzheimer's disease group. However, even though some concomitant vascular dementia pathology might exist in the reviewed Alzheimer's disease groups, this does not change our conclusions: by influencing BP and hyperlipidaemia, it may be possible to reduce the risk of both Alzheimer's disease and vascular dementia in the brain.

The issue of vascular pathology versus Alzheimer's disease is, in fact, even more complicated if we take into account the fact that the very essence of Alzheimer's disease is not yet fully determined. The significance of amyloid-β plaques or neurofibrillary tangles, the classic pathological features of Alzheimer's disease, is not known (are they the cause or consequence of the disease?).[52,53] Furthermore, there is no apparent pathophysiological reason to expect that cerebrovascular and Alzheimer's processes are mutually exclusive.[54] In particular, in old age, vascular pathology causes or contributes to the dementia syndrome very often, and mixed pathology is surely common.[53,55] There is also some evidence that stroke and Alzheimer's disease occur in the same patients more frequently than would be anticipated by chance.[37] This is no surprise if we assume that Alzheimer's disease and stroke share the same risk factors, but it rather supports our theory.

4. Conclusion

Elevated BP and serum cholesterol levels seem to have an important role in the development of Alzheimer's disease as suggested by both epidemiological studies and studies that have reported a decreased incidence or prevalence of Alzheimer's disease in patients receiving antihypertensive or lipid-lowering drug treatments. These findings are also supported by experimental studies. Together, these data suggest that there may be a true causal relationship between these proposed risk factors and Alzheimer's disease.

At present, the exact mechanisms by which elevated BP and cholesterol levels may increase the risk of Alzheimer's disease, and their relative importance in the pathogenesis of Alzheimer's disease, are unknown. Nevertheless, there is a convincing body of evidence to suggest that these vascular risk factors are important for the development of Alzheimer's disease in a proportion of patients. This may be considered as sufficient evidence to emphasise the need for clinical interventions to control these risk factors more effectively. Early interventions aimed at reducing these cardiovascular risk factors may have a profound impact on the future incidence and prevalence of Alzheimer's disease. Importantly, there are already clear indications that hypertension and hypercholesterolaemia should be treated (i.e. there is a need to treat these risk factors anyway in view of cardiovascular sequela), as well as a number of means available for the treatment of hypertension and hyperlipidaemia. With appropriate treatment, not only is the patient's chance of escaping cardiovascular morbidity and mortality increased, but his/her chance of escaping Alzheimer's disease may increase as well.

Acknowledgements

The authors are grateful for grants from the Academy of Finland (37573 and 63645) and the EVO (477268 and 5510) and have no conflicts of interest that are relevant to the contents of this article.

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