

Hypertension, cognitive decline, and dementia: an epidemiological perspective

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Hypertension is a known risk factor for stroke, and thus for vascular dementia. However, recent large observational studies have suggested that high blood pressure may also play a role in Alzheimer's disease. The mechanisms linking hypertension to Alzheimer's disease remain to be elucidated, but white matter lesions seen on cerebral magnetic resonance imaging appear to be a good marker of this association. It is not yet clearly established whether lowering blood pressure reduces the risk of white matter lesions and dementia, so large trials dealing with this question are eagerly awaited. These future trials could confirm the hope that, by lowering blood pressure, we may have a preventive treatment for dementia. This issue is of major importance, as the number of cases of dementia is expected to rise sharply in the near future.

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Dementia is one of the major causes of loss of autonomy, and the main reason for the institutionalization of the elderly. Epidemiological studies conducted in the last 10 years have shown that the prevalence of dementia is close to 5% in the population over 65 years of age. These studies have also shown that its prevalence increases sharply with age, and as a result of the expected shift in population demographics, the incidence and prevalence of dementia are expected to increase dramatically over the coming decades. The number of demented patients worldwide is projected to increase from 24.3 million in 2001 to 81.1 million in 2040.¹ Significantly, the vast majority of new cases are expected to appear in developing countries. For example, the number of demented persons in China and India will increase by 300% during this period.¹ Prevention and management of dementia are therefore a major public health challenge in the majority of countries around the world.

As a general rule, the occurrence of dementia is not a sudden phenomenon. It is the final stage of cognitive deterioration, the speed of which varies from one individual to the other. However, even in cases where its development is rapid, the process is measured in terms of months. Taking into account the life expectancy of individuals at risk, retarding the development of dementia for a few months may have important consequences on the prevalence of dementia.²

Such expectations have been raised in recent years with the discovery of a relationship between hypertension and dementia. Overall, published studies suggest that high blood pressure increases the risk of cognitive decline and dementia, and therefore, that lowering blood pressure might reduce this risk. This paper will review the evidence for this, and will discuss some of the important questions that remain unanswered.

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Selected abbreviations and acronyms

ACE	<i>angiotensin-converting enzyme</i>
AD	<i>Alzheimer's disease</i>
MMSE	<i>Mini Mental State Examination</i>
MRI	<i>magnetic resonance imaging</i>
PROGRESS	<i>Perindopril pROtection aGainst REcurrent Stroke Study</i>
SCOPE	<i>Study on COgnition and Prognosis in the Elderly</i>
SHEP	<i>Systolic Hypertension in the Elderly Program</i>
Syst-Eur	<i>Systolic Hypertension in Europe Trial</i>
WML	<i>white matter lesions</i>

Hypertension and cognitive decline: evidence from observational studies

It has been known for decades that there is a direct, causal relationship between high blood pressure and the risk of stroke, and therefore the risk of dementia (*Figure 1*). It is common knowledge that large strokes or multiple strokes contribute directly to cognitive decline and to the risk of dementia, consequently called vascular dementia. However, it is only in the past 10 years that studies have reported that hypertension may be related to cognitive decline and dementia without the occurrence of a stroke.

Hypertension and stroke-related dementia: a well-established relationship

Hospital- and population-based studies have firmly established that dementia is more frequent in patients with stroke than in patients without.³⁻⁸ Cognitive assessment performed 3 months after stroke revealed that 20% to 30% of patients are demented.^{7,9,10} In one of the largest clinical series of 453 patients who were examined 3 months after their stroke, 26% were demented.¹¹ It is estimated that stroke multiplies the risk of dementia by a factor of two to five, thus constituting one of the strongest risk factors for dementia.^{3,5,10,12,13} The strength of this association suggests a causal link between stroke and dementia, although numerous other factors influence this relationship, some pertaining to the patient—such as age, level of education, cognitive level before stroke, white matter lesions on magnetic resonance imaging (MRI), Apolipoprotein E4 (*ApoE4*) allele, etc—and others to the stroke itself—mainly its size, severity, and location. Interestingly, in the few studies that have included a clas-

sification of dementia, typical vascular dementia represented only 57%¹¹ to 64%⁷ of all dementias with stroke, thus suggesting that a significant proportion of stroke-associated dementias may be classified as Alzheimer's disease (AD) or mixed dementia. This was confirmed in population-based studies in Rochester and New York, where a 50% to 60% increase in AD in individuals with stroke compared with those without was observed.^{5,14} These data were interpreted as meaning that the occurrence of a stroke may actually unmask ongoing AD. This hypothesis was also lent support by studies showing that prestroke cognition is altered in 15% to 20% of patients with a post-stroke dementia.^{15,16} The effect of this interaction between neurodegenerative factors or lesions and stroke on the risk of dementia has been demonstrated in the Nun study.¹⁷ In this autopsy study, participants who had the neuropathological hallmarks of AD and at least one lacunar stroke had a risk of clinical dementia multiplied by a factor of about 20 compared with those with the hallmarks of AD but no lacunar stroke.

To summarize, even if the relationship between stroke and dementia is not disputed, it appears that the question of the type of dementia is more complex than initially believed. In many cases, poststroke dementia might be related to pre-existing neurodegenerative lesions. Conversely, some small and not always clinically noticeable infarcts may precipitate individuals towards a clinically conspicuous AD. What is not yet understood is the extent of these phenomena. If they were not so infrequent, the relevance of the existing classification of dementia, based on a clear-cut separation of vascular dementia and AD, would undoubtedly be questioned.

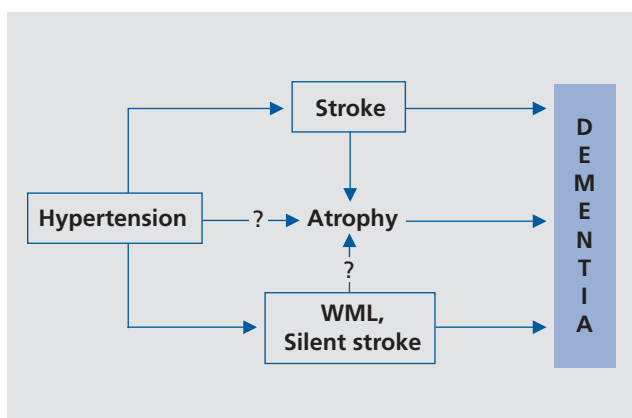


Figure 1. Diagrammatic representation of the consequences of hypertension on the brain. WML, white matter lesions

Hypertension and cognitive decline unrelated to stroke

Several studies have shown an inverse association between blood pressure and cognitive function without the occurrence of a stroke (*Figure 1*). In the Framingham Heart Study, Elias et al examined cognitive function and memory performance as related to initial blood pressure measurement over a 12-to 14-year period.¹⁸ Among 1702 subjects, cognitive performance was inversely correlated with initial systolic and diastolic blood pressure readings: the higher the blood pressure, the lower the cognitive performance. In the Honolulu-Asia Aging Study, in which 3735 Japanese-American male subjects living in Hawaii were enrolled, elevated systolic blood pressure in midlife predicted future reduced cognitive function. A 10-mm Hg increase in systolic blood pressure was associated with a significantly increased risk of both intermediate and poor cognitive function. This relationship remained after adjustment for stroke, coronary heart disease, and subclinical atherosclerosis.¹⁹ Our group conducted a longitudinal study in 1373 older adults (aged 59 to 71 years), the EVA study, to examine whether baseline hypertension and use of antihypertensive medication predicted cognitive decline at a 4-year follow-up assessment.²⁰ We found a relationship between cognitive decline and a history of hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 95 mm Hg), and we also discovered that the risk was the highest in patients with untreated hypertension. Hypertensive subjects receiving adequate treatment had no increased risk of cognitive decline compared with normotensive subjects.²⁰ In another prospective, longitudinal, population-based study, it was also found that among 2068 elderly individuals, subjects aged 65 years or older were more likely to make errors on a mental status questionnaire when their systolic blood pressure taken 9 years earlier was at least 160 mm Hg.²¹ Other studies have not found any association between high blood pressure and cognitive function.²²⁻²⁶ This inconsistency has been attributed to the selection of populations investigated, differences between the methods used to assess cognitive function, and perhaps a misunderstanding of the synchronicity in the development of hypertension and cognitive impairment. However, a majority of cross-sectional and longitudinal studies have found a deleterious effect of high blood pressure on cognition.^{27,28}

With regard to dementia, several studies have reported a similar association between high blood pressure and the risk of dementia. In a longitudinal study in Sweden, a sig-

nificant link was found between the presence of high systolic and diastolic blood pressures and the development of dementia 10 to 15 years later.²⁹ Similar findings were reported in other studies, such as the Honolulu-Asia Aging Study,³⁰ a Finnish study with a 21-year long follow-up,²⁸ and the Kaiser Permanente study.³¹ In comparison with the study of simple cognitive decline, there is a greater number of studies that show no association between dementia and high blood pressure, and some even suggest that dementia is associated with low blood pressure.^{32,33} This could be explained, in full-blown dementia, by the neuronal depopulation of deep brain structures involved in the control of blood pressure or by the apathy of severely demented individuals who may have lessened their activity and consequently their blood pressure.

Antihypertensive treatment was sometimes found to be protective in observational studies. In a community cohort study of 1810 persons aged 75 years or older, the prevalence of dementia was significantly lower among patients being treated for hypertension than among those not taking antihypertensive medications ($P < 0.001$).³⁴ In The Honolulu-Asia Aging Study, early and aggressive blood pressure control lessened the likelihood of cognitive impairment in later life.¹⁹ Similarly, in the EVA study, hypertensive subjects receiving adequate treatment had no increased risk of cognitive decline compared with normotensive subjects.²⁰

Randomized trials of blood pressure-lowering drugs on the risk of dementia

Prevention of dementia in stroke patients: the PROGRESS study

Blood pressure-lowering therapy with the long-acting ACE inhibitor perindopril combined with the diuretic indapamide reduces the risk of poststroke dementia by one third and the risk of severe cognitive decline by nearly one half, according to the results from the PROGRESS study (Perindopril pROtection aGainst REcurrent Stroke Study).³⁵ PROGRESS was a randomized, double-blind, placebo-controlled trial that enrolled 6105 men and women, with a mean age of 64 years, with prior stroke or transient ischemic attack (TIA), from 172 institutions in 10 countries in Asia, Australia, and Europe. Participants were randomized to active treatment ($n=3051$) or placebo ($n=3054$).^{36,37} Active treatment was comprised of perindopril 4 mg

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daily for all participants, along with 2.5 mg daily of the diuretic indapamide (2 mg in Japan) in patients in whom a diuretic was neither specifically indicated nor contraindicated. The main results of PROGRESS³⁸ were that active treatment with perindopril alone or with indapamide reduced blood pressure by 9/4 mm Hg over 4 years of follow-up, and was associated with an overall reduction of 28% in the risk of recurrent strokes (the primary outcome of the study) compared with placebo ($P<.0001$ among hypertensive and nonhypertensive patients with a history of stroke or TIA). Active treatment also reduced the risk of total major vascular events by 26%. Combination therapy with perindopril plus indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43%. One of the secondary outcomes of PROGRESS was dementia and severe cognitive decline. During the follow-up period of 4 years, dementia (diagnosed according to DSM-IV criteria) and severe cognitive decline (a drop of ≥ 3 points in the Mini Mental State Examination [MMSE]) were assessed. Median MMSE score at baseline was 29 (range, 27 to 30); a large proportion of patients (41%) had good cognitive function (MMSE ≥ 30), but 16% had cognitive impairment (MMSE < 26). Over 25% of patients screened positive for dementia (768 and 812 in the active treatment and placebo groups, respectively). After independent assessment by an expert in dementia, 410 patients were identified as having dementia (equivalent to an incidence of 17 per 1000 patient-years), of whom 108 had dementia preceded by a stroke. Cognitive decline was identified in 610 patients (incidence of 25 per 1000 patient-years), of whom 134 had had a previous stroke. Overall, there was a nonsignificant (12% (range, -8% to 28%]) reduction in the risk of dementia in the active treatment group. Evaluation within the two dementia subgroups (with or without prior stroke), however, showed a significant reduction of 34% ($P=.03$) in the risk of dementia with active treatment in patients with prior stroke and a 1% reduction in patients without prior stroke. A similar pattern was observed for cognitive decline, with an overall risk reduction of 19% ($P=0.01$) with active treatment overall, but a significant risk reduction of 45% ($P<.001$) with active treatment in patients with prior stroke and a 9% reduction in patients without stroke. Combination therapy was more effective in reducing the risk of dementia (23%) than monotherapy (-8%), although there was no statistical difference between regimens (P for homogeneity, 0.1) In patients with no cognitive

impairment at baseline (84%), active treatment reduced the risk of dementia by 31%, but there was no effect in patients with cognitive impairment at baseline (-3%). Among the patients without cognitive impairment at baseline, a 50% reduction in the risk of dementia was observed in those with prior stroke, compared with a 16% reduction in those without stroke.

Trials in hypertensive patients without stroke

Four large-scale randomized controlled trials using blood pressure-lowering agents have reported the effects of treatment on the risk of dementia or measures of cognitive function.³⁹⁻⁴² While three trials identified no clear effect of the treatment under study on the risk of dementia^{39,42} or on cognitive function,^{40,42} one reported a significant benefit from treatment on the risk of dementia.⁴¹

In the UK Medical Research Council's trial in older hypertensive patients, there was no apparent effect of treatment on any measure of cognitive impairment.⁴⁰ Similarly, in the Systolic Hypertension in the Elderly Program (SHEP),³⁹ active treatment had no discernible effect on the incidence of dementia. However, a recent reanalysis suggests that differential dropout rates in active treatment and placebo groups may have introduced a bias leading to this conclusion.⁴³

The most exciting data with regard to the prevention of dementia by lowering blood pressure have come from the Syst-Eur trial.^{41,44} This trial was a double-blind, placebo-controlled trial of nitrendipine, a calcium antagonist, with the addition of enalapril, hydrochlorothiazide, or both, titrated or combined as needed to reduce systolic blood pressure by at least 20 mm Hg so as to reach a target of < 150 mm Hg in over 4000 patients aged over 60 years. Syst-Eur included a dementia substudy in a subset of 2418 patients (1180 in the placebo group and 1238 in the active-treatment group). At the end of the trial, which was stopped prematurely after a median follow-up of 2 years because the preplanned interim analyses demonstrated a significant benefit for stroke, 1861 patients remained on double-blind treatment; 60% received nitrendipine alone, 32% received nitrendipine plus enalapril, and 15% received these two drugs plus hydrochlorothiazide. Dementia was diagnosed in 21 cases in the placebo group and in 11 cases in the active treatment group, resulting in a 50% reduction in the incidence of dementia in the active arm. Interestingly, the majority of dementia cases were of AD and not vas-

cular dementia. This remarkable finding should, however, be interpreted with caution because of the small number of outcome events. As a result of this limited power, the possible impact of blood-pressure lowering can extend from having no effect to a massive 76% reduction in the risk of dementia. Moreover, the large number of participants who were lost to follow-up further undermines the validity of the study.

In another randomized trial, the Study on Cognition and Prognosis in the Elderly (SCOPE), no treatment effect on cognition was observed.^{42,45} SCOPE was a prospective, double-blind, randomized, parallel-group study conducted from 1997 to 2002, in which 4964 patients aged 70 to 89 years, with SBP 160 to 179 mm Hg and/or DBP 90 to 99 mm Hg (untreated or thiazide-treated) and MMSE test score ≥ 24 , were assigned to receive candesartan or placebo with open-label active antihypertensive therapy added if necessary. No significant difference was observed in mean final MMSE score between the candesartan group (final score 28.0) and the control group (final score 27.9) ($P=.20$), and the proportion of patients who had a significant cognitive decline or who developed dementia was not different in the two treatment groups.⁴² However, due to ethical concerns, this study was finally redesigned to compare effects between the candesartan-based treatment and the usual antihypertensive therapy regimens and, as a result, the reduction in blood pressure was limited (*Table I*).

In summary, there are still very few large trials that have assessed the prevention of dementia by blood pressure-lowering drugs (*Table I*). PROGRESS is the only study that has assessed the risk of dementia in patients with stroke. It reports a reduction in the risk of poststroke dementia and no clear effect on the risk of dementia

without stroke.³⁵ The most convincing trial to date in non-stroke patients, Syst-Eur, is hampered by the relatively small number of cases. In an open extension of the follow-up the results of the main study were confirmed, with a doubling of the number of cases.⁴⁶ However, special caution is needed to interpret these results because of the limitations and the potential biases of an open follow-up. A large and specifically designed trial is therefore needed to confirm and to quantify the reduction of the risk of dementia by blood pressure-lowering drugs in hypertensive subjects.

Mechanisms of the relationship between hypertension and cognition when there is no stroke: the white matter lesion hypothesis

The mechanisms by which high blood pressure can operate at the cerebral level are widely unknown. Recently, the development of cerebral imaging and more particularly of MRI has shown that silent strokes, and more broadly, white matter lesions (WML) are common, in particular in patients with hypertension and in the elderly (*Figure 2*).

WML: definition and risk factors

WML are areas of high signal on T2-weighted images located in the cerebral white matter, and among them, silent strokes may be singled out by their low signal on T1-weighted images. These lesions share the same risk factors as stroke, mainly age⁴⁷⁻⁵³ and hypertension.⁵⁴⁻⁵⁸ Some studies have shown that a sustained high blood pressure level increases the risk of WML, suggesting that there was a dose-response relationship.^{56,57} The level of

Study	Sample size	SBP/DBP difference (active vs placebo)	Drug tested	Duration of follow-up	Reduction in the risk of dementia	P value
SHEP ³⁹	4736	-12/4 mm Hg	BB \pm diuretic	4.5 years	16%	NS
Syst-Eur ⁴¹	2418	- 8.3/3.8 mm Hg	CCB \pm ACE \pm diuretic	2 years	50% (0-76%)	0.05
PROGRESS ³⁵	6105	- 9 / 4 mm Hg	ACE \pm diuretic	4 years	All dementia: 12% (8-28%) Dementia with recurrent stroke: 34% (3-55%)	NS 0.03
SCOPE ⁴²	4964	- 3.2 / 1.6 ^m mm Hg	ARB	4 years	7%	NS

Table I. Main randomized trials on antihypertensive drugs and the risk of dementia. SBP, systolic blood pressure; DBP, diastolic blood pressure; BB, β -blocker; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type1 receptor blocker; NS, nonsignificant

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blood pressure also seems to play a role, the highest blood pressure values being associated with the higher grades of WML.⁵⁹ This aspect of dose-response in terms of duration and level of exposure is an important argument to suggest that the relationship between high blood pressure and WML may be causal, as it is for stroke. The mechanisms leading to WML are not yet fully understood, but degeneration of small-caliber arteries (arteriosclerosis) has been consistently found,⁶⁰⁻⁶² as well as a reduced cerebral blood flow⁶³⁻⁶⁶; these are both known consequences of high blood pressure on the brain.⁶⁷⁻⁶⁹ Therefore, it is generally assumed that WML are a marker of a chronic state of cerebral ischemia in hypertensive patients.

Consequences of WML

One general hypothesis is that the accumulation of lesions in the white matter can lead to a subsequent cognitive deterioration by disconnection of cortico-subcortical pathways. Several studies have indeed shown that WML are associated with cognitive impairment^{47,52,53,59,70-72} and with dementia⁷³⁻⁷⁵ (Figure 1). Several aspects are, however, still poorly understood: What is the relative importance of the location, type, and extent of WML on the risk of cognitive impairment? Are there major effect modifiers on this relationship, such as the *ApoE* polymorphism and education level? Are WML associated with cortical atrophy? If yes, as suggested by some studies,⁷⁶⁻⁷⁸ what is the relative importance of both regarding the risk of cognitive impairment? Some of these ques-

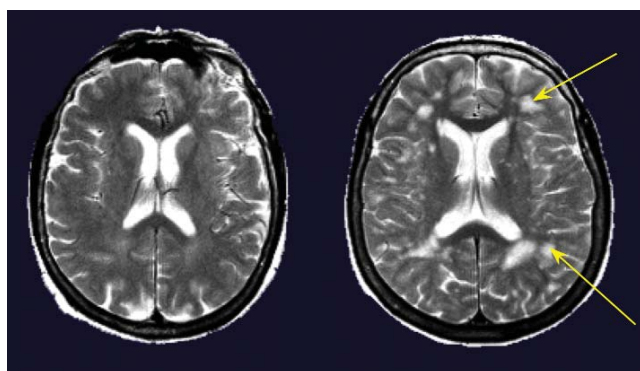


Figure 2. White matter lesions on cerebral MRI. Cerebral MRI of two women 67 years of age without (on the left) and with (on the right) hypertension. The subject with hypertension had several deep and periventricular white matter lesions (arrows). MRI, magnetic resonance imaging

tions have already been addressed, though very often with small series of selected patients. Further, the evaluation of WML is highly variable across studies, and no clear consensus has yet emerged to date.

WML have also been found to be associated with gait disturbances and a higher risk of falls⁷⁹⁻⁸³ and symptoms resembling Parkinson's disease,⁸⁴⁻⁸⁶ as well as a higher risk of stroke^{87,88} and depression.⁸⁹⁻⁹³ It is therefore not an overstatement to say that WML—at least when their load is elevated—are guilty of accelerating aging of the brain. Trying to control their aggravation is therefore an important goal.

Preventing the evolution of WML: the PROGRESS-MRI study

This was a substudy of the PROGRESS trial described above. In this substudy,⁹⁴ we analyzed data gathered from 192 people (average age 60) recruited in 10 centers in France. Each participant had a brain MRI at baseline, which was repeated after an average follow-up of 36 months. At baseline, a neuroradiologist examined each scan and determined that 42% of participants had no WML; 26% had mild WML, 13% had moderate WML and 19% had severe WML. Eighty-nine patients were in the active treatment arm, and 103 were on placebo. About half of the subjects were already being treated for high blood pressure. At the time of the second MRI, blood pressure had significantly decreased by an average of 11.2 mm Hg systolic and 4.3 mm Hg diastolic. In order to limit the variability between the two exams attributable to the MRI technique (position of the head of the patient, different slicing, etc), we performed an automatic registration and segmentation of both MRI exams after their storage in an Object-Oriented Relational Database. By doing so, we made both exams as comparable as possible, and an independent observer, blinded to the data and the order of the MRI exams, would be able to compare them precisely and detect and measure any new lesion. Overall, the risk of new WML was reduced by 43% in the treatment group compared with the placebo group, although the difference did not reach significance ($P=0.10$). The volume of new areas of WML in the treatment group was one fifth of that in the untreated group (0.4 cubic mm versus 2 cubic mm, $P=0.012$). The most striking difference was noted in the 27 patients who already had severe WML at the first MRI. In these subjects, no new areas of abnormality developed in those in the treatment group, compared with an

average of 7.6 cubic millimeters of new WML in patients on placebo ($P=0.001$).

This study showed, for the first time, that it is possible to limit the development of WML by lowering blood pressure, even though the number of subjects was rather small. As result of this low power, there was not sufficient power to study simultaneously the impact of treatment on cognition in this sample. Further studies are needed to confirm these results in larger and independent samples. Also, studies should be performed in patients who do not have a past history of cerebrovascular disease.

Tentative conclusions and future prospects

There is no doubt that high blood pressure is associated with cognitive deterioration and dementia, independently of the occurrence of a stroke. Conflicting results come in part from the various ways of testing cognition and defining cognitive decline, and the lack of precisely diagnosing dementia in its early stage. Another, and yet unsolved, issue is the modification of this relationship with age. It is likely that the risk of cognitive deterioration related to high blood pressure decreases with increasing age. A similar modification of the risk with age is observed in the relationship between hypertension and stroke. Further, there appears to be spontaneous lowering of blood pressure at the advanced stage of dementia, probably through neuronal depopulation in the centers regulating blood pressure, which renders the relationship even more complex. Finally, the true relative risk of dementia associated with hypertension is probably relatively modest compared with other stronger risk factors for dementia like age, education, and the *ApoE* polymorphism. Therefore, some degree of fluctuation is not unexpected when estimating this risk, and some of the controversial results could thus be explained.

Despite these difficulties, clarifying this relationship remains of major importance. With the ageing of our societies, we are facing an epidemic of dementia for which we have no curative or preventive treatment. In this context, even a modest reduction in the risk would have important consequences. Moreover, even if high blood pressure is associated with a moderate relative risk of dementia, its very high prevalence means that the risk of dementia attributable to high blood pressure may be high, and that improved control of hypertension may translate into a dramatic reduction in the number of cases of dementia.⁹⁵

Unanswered questions

What is the true magnitude of the relationship?

The data are still insufficient, and we definitively need more population-based studies in the elderly in order to accurately estimate the risk of dementia attributable to high blood pressure and other vascular factors. Some of the existing large population-based studies in this domain should also combine their efforts with a view to producing an exact measure of this risk.

Is it possible to identify individuals or groups at high risk?

It is likely that the effect of high blood pressure on the brain varies dramatically between individuals, even among hypertensive patients. Those at high risk of hypertension-related cognitive decline or dementia would benefit the most from accurate control of their hypertension. Again, these high-risk groups can be properly identified only in large observational studies with a long follow-up.

Are WML an appropriate marker of the poor tolerance of high blood pressure by the brain?

The answer is most likely positive, but several issues on the true mechanisms linking WML to cognition remain unresolved, in particular regarding their characteristics: location, size, signal intensity, etc. In addition, what is not well understood either is the natural history of WML. Results from a few studies suggest that some patients have a rapid increase in their WML load and that they would be those who have a higher risk of severe cognitive decline, but this remains to be confirmed.

These questions are important, and must be answered to improve our understanding of the relationship between hypertension and dementia. However, it is also possible to state that we have enough data at hand to set up a clinical trial on the reduction of the risk of dementia by lowering blood pressure. This trial, specifically designed to study dementia, should be very large so as to produce a significant number of cases with the longest follow-up as possible. Among some other important variables, the investigators of this trial would have to choose the type of patients who should be included: old-old patients are more exposed to a short-term risk of dementia, but blood pressure-lowering drugs might be

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less effective in these patients than in young-old patients who are, in turn, less prone to dementia. Demonstrating a treatment effect in the youngest hypertensive patients would require a much larger number of patients or a longer follow-up. The choice of the type of drug could also be important, as it is not yet known if the protective effect observed is uniquely due to the lowering of blood pressure or if there is a class effect of a given antihypertensive agent. A meta-analysis⁹⁶ suggests that calcium antagonists are more effective than other drugs in reducing the risk of stroke in hypertensive patients. Whether this apparent class effect could also apply to the risk of dementia is an open question. Finally, an important decision is whether or not to perform MRI scans on part of the sample or on the entire sample. The data from MRI exams would be of great value in con-

firming the impact of the blood pressure-lowering drug on the brain and in understanding the variability of this impact across categories of patients.

The study of the epidemiology of dementia and cognitive deterioration has now completed its first phase, which began in the early 1990s and provided extensive descriptive data. Given the growing epidemiological and clinical evidence for the implication of vascular factors in the risk of dementia, the identification and control of these factors in middle-aged and elderly individuals may represent an important approach for decreasing the incidence of dementia. This could be demonstrated properly only through large randomized trials. One can expect that, as has occurred with coronary heart disease, the second phase of the study of the epidemiology of dementia will be devoted to such trials. □

Hipertensión, déficit cognitivo y demencia: una perspectiva epidemiológica

La hipertensión arterial es un factor de riesgo conocido para el accidente vascular encefálico y en consecuencia para la demencia vascular. Sin embargo, extensos estudios observacionales recientes han sugerido que la presión arterial elevada puede jugar también un papel en la Enfermedad de Alzheimer. Los mecanismos que relacionan la hipertensión con la Enfermedad de Alzheimer aun deben ser dilucidados, pero las lesiones en la sustancia blanca que se han observado en la resonancia magnética cerebral parecen ser buenos marcadores de esta asociación. Aun no está claramente establecido que la reducción de la presión arterial disminuya el riesgo de lesiones en la sustancia blanca y de demencia, por lo que se espera con gran ilusión que grandes ensayos clínicos traten de aclarar esta pregunta. Estos futuros ensayos clínicos podrían confirmar la esperanza que, al reducir la presión arterial, se pueda contar con un tratamiento preventivo para la demencia. Este tema es de la mayor importancia ya que se espera que el número de casos de demencia aumente marcadamente en un futuro cercano.

Hypertension, déclin cognitif et démence : une perspective épidémiologique

L'hypertension est un facteur de risque connu d'accident vasculaire cérébral et donc pour la démence vasculaire. Cependant, le rôle éventuel d'une pression artérielle élevée dans la maladie d'Alzheimer a été évoqué dans des études récentes observationnelles portant sur de grands effectifs. Les mécanismes liant l'hypertension à la maladie d'Alzheimer demandent à être approfondis mais des lésions de la substance blanche vues à l'IRM (imagerie par résonance magnétique) semblent être un bon marqueur de cette association. Il n'est pas encore clairement établi que la baisse de la pression artérielle diminue le risque de lésions de la substance blanche et de démence. De larges études consacrées à cette question sont éminemment attendues. Elles pourraient confirmer l'espoir d'un traitement préventif de la démence par diminution de la pression artérielle. Il s'agit d'un problème d'importance majeure du fait que le nombre de cas de démence est amené à augmenter considérablement dans un futur proche.

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