Is Hypertension Associated With an Accelerated Aging of the Brain?

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One of the first studies to examine the question of a potential negative impact of hypertension on the brain was published in 1971 in Science.1 Subsequently, many studies have been published, mainly on the relationship of blood pressure (BP) with cognitive performance, cognitive decline, and dementia.2 Their results were sometimes contradictory, some studies even suggesting that high BP could protect against the risk of dementia. This apparent contradiction created some confusion and a sense that this issue should not deserve much attention. The accumulation of data from high-quality population-based studies has helped us to decipher this riddle. Indeed, they have shown that the impact of hypertension on the brain strongly depends on when BP is measured in life. High BP in middle age is a risk factor for dementia, but not when measured at an old age. This age-dependent effect of exposure and the fact that, to fully evaluate its impact, hypertension should be assessed several decades before the onset of dementia have made it remarkably more complex to study the role of hypertension on the brain.

Because of global aging, the number of dementia cases is skyrocketing around the world. The last World Health Organization report estimates that in 2010, 7.7 million persons have developed dementia, 1 new case every 4 seconds.3 The estimated at 35.6 million in 2010 and is projected to reach 115.4 million in 2050. This ongoing epidemic of dementia and the absence of any preventive or curative treatment revived interest in studying modifiable risk factors of dementia, even if this relationship is complex as for hypertension. Indeed, simulation studies have shown that delaying by just a few months the entry into the clinical phase of the disease could enable, at the population level, a dramatic decrease in new dementia cases after a few decades.4

Several population-based cohort studies have shown that vascular risk factors are associated with the risk of not only vascular dementia but also Alzheimer disease (AD). These data have raised the hypothesis that the vast majority of cases of dementia are a mix of vascular injury and neurodegenerative lesions.5 They have raised the hope that a better control of vascular factors, including hypertension, could help reduce the incidence of dementia. As explained in this article, the few BP-lowering trials that have included dementia or decline in performance on cognitive tests as an outcome have not confirmed this hypothesis although they were not designed properly for responding to this complex issue.6

The development of brain MRI has had a significant impact on the study of vascular brain injury (VBI) in dementia.7 Population-based studies in elderly individuals have shown that vascular lesions are highly prevalent in the community, and that when their burden is important, they are associated with increased risk of stroke, dementia, cognitive impairment, and other neurological dysfunctions.

Although in the past 20 years major progress has been made in understanding the role of vascular factors on the brain, several major questions remain unanswered. In this review, we summarize current evidence on the real impact of hypertension on VBI, cognitive decline, and dementia at the individual and population level, effects of antihypertensive therapy on these outcomes, the identification of individuals at high risk of VBI, and the mechanisms leading to VBI. Dementia is usually not of sudden onset and is often heralded by a deterioration of cognitive functions. Cognitive decline over time is therefore a major indication of an ongoing dementing process and is included in this review. We also provide some hints for clinicians who are increasingly facing the question of how to manage patients with apparently asymptomatic MRI-defined VBI.

High Blood Pressure, Stroke, and Dementia

Hypertension, Risk of Stroke, and of Related Dementia

Hypertension is the most powerful acquired risk factor for stroke and, because of its high frequency, about half of all strokes would be attributable to hypertension.6

The direct robust association between hypertension and the risk of stroke and, thus, of poststroke dementia, was established several decades ago. Hospital-based and population-based studies have shown that dementia is more frequent in individuals with a history of stroke than those without.5,8 It is estimated that stroke increases the risk of dementia by a factor of 2 to 5, making stroke one of the greatest risk factors for dementia.

The question of the mechanisms underlying the relationship between stroke and dementia seems to be complex. Indeed, in many cases, poststroke dementia may be linked to pre-existing...
neurodegenerative lesions. The Nun study was one of the first to highlight this interaction between neurodegenerative and vascular lesions on the risk of dementia. In this study, based on autopsy findings, the presence of a small lacunar infarct was found to multiply the risk of clinical dementia by a factor of 20 in people meeting the neuropathological criteria for AD.9

Many clinical trials and meta-analyses have demonstrated that lowering BP reduces the risk of stroke in primary and in secondary prevention.10,11 However, the evidence that lowering BP may reduce the risk of stroke-related cognitive decline or dementia is much weaker. In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial, 6105 patients with a history of stroke or transient ischemic attack were treated with an angiotensin-converting enzyme inhibitor with or without a diuretic compared with a placebo. The risk of poststroke dementia was decreased by one third and the risk of poststroke severe cognitive decline was almost halved in the active treatment arm.12 From a public health perspective the most urgent task is to improve stroke prevention through well-established therapeutic strategies.

**Hypertension and Cognitive Impairment or Dementia Unrelated to a Stroke**

High BP seems to have other effects on the brain, especially through the development of covert VBI, which settles insidiously but is common in the community, as revealed by MRI performed in large population-based samples.

**Evidence From Observational Studies**

The question of brain damage regardless of the occurrence of a stroke has been suspected for a long time, and many studies suggest that high BP is a risk factor for poorer cognitive functioning and dementia.15,17 In the Framingham Heart study, cognitive functions and memory were analyzed as a function of midlife arterial pressure measured 12 to 14 years earlier and cognitive performance was found to be correlated inversely with initial BP measurements.14 When exploring cognition by domains, hypertension seems to be associated particularly with worse performance and more rapid decline in executive function and processing speed,18,19 whereas associations with memory performance are less marked. Of note, associations of hypertension with cognitive function are not consistent across all published studies.20

Several observational studies have analyzed the relationship between hypertension and the risk of dementia. In a Swedish study among individuals nondemented at the age of 70 years, those who developed dementia during a follow-up period of 10 to 15 years had a higher systolic BP (SBP; mean, 178 versus 164 mm Hg) and diastolic BP (101 versus 92) at the age of 70 years compared with those who did not get demented.15 Similar results have been reported in other studies, such as the Honolulu-Asia Aging Study,16 a Finnish study with a 21-year follow-up period,17 and the Kaiser Permanente study.21 However, some studies did not report any association.22,23

**Midlife Versus Late-Life Hypertension**

Systematic reviews have suggested that the association of BP with cognitive decline and dementia is complex and seems to differ according to age and follow-up duration.20,23 Overall, the relationship is stronger in studies with a long follow-up and with BP measurement in midlife.22 In the Honolulu Asia Aging Study, among participants who did not report taking antihypertensive medication in midlife, 27% of dementia cases could be attributed to SBP >120 mm Hg.16 In contrast, studies with a short follow-up or cross-sectional studies on BP measured in late-life and dementia are less consistent. In these studies, hypertension does not seem to be associated with an increased risk of dementia and, in some, dementia was even associated with lower BP.21,24 One possible explanation for this last observation is that, in advanced forms of dementia, neuronal depopulation of brain stem structures involved in controlling BP or the apathy of demented patients, who tend to be less active or not to eat properly, may decrease arterial pressure.

There are several possible explanations for the observed age-dependent effect of exposure. First, exposure to hypertension in midlife probably better reflects the total exposure to elevated BP throughout a lifespan. Second, in older people, vascular risk factor measurements may be modified by concomitant chronic diseases inducing weight loss, BP drop, and other metabolic changes. Third, associations with late-life BP measurements may be modified by survival bias, because of premature death of individuals exposed to high BP levels. Fourth, increased intake of medications in late-life could modify associations between vascular risk factors and dementia.25 Finally, in older individuals, the impact of vascular disease may be overwhelmed by effects of AD pathology or age-related neurodegenerative changes. This major age-dependent effect modification adds an important degree of complexity to deciphering the relationship between BP and dementia. The variety of cognitive tests, the lack of highly reliable biomarkers for dementia, the variability of BP between measurements and its evolution with age, and the survival biases in relation to age and to BP, further contribute to explaining why no clear pattern has yet emerged on this important question. For other clinical expressions of brain aging, such as motor-impairment and parkinsonism, data on the role of hypertension are scarce26 and the level of evidence is even weaker than for cognitive impairment and dementia.

Overall, the impact of hypertension on the brain seems to be the result of a complex interaction mixing several important components: (1) timing: there seem to be critical periods of life during which hypertension has a stronger impact; (2) duration: it is likely that a longer exposure would result in a higher level of damage; (3) intensity: highest BP levels are associated with increased frequency and severity of lesions; (4) other BP components and consequences yet to be explored or discovered fully, such as variability, extreme deeping, and arterial stiffness; and finally (5) individual characteristics at many different levels including damage of the large and small vessels irrigating the brain and the sensitivity of the latter to ischemia. This situation is likely to be similar for other factors like diabetes mellitus.

**Antihypertensive Agents and Risk of Dementia**

**Observational Studies**

Several longitudinal studies have been published on the impact of antihypertensive drug use on the risk of dementia without stroke,2,27 and their results were inconsistent, with no
association in some studies, whereas in others there was a decreased risk of AD among those taking antihypertensive treatment. The strongest results were usually found in studies with a long duration of treatment.

**Randomized Trials**

No clear pattern emerges from randomized trials of antihypertensive drugs that have included an evaluation of dementia or cognitive function. Four trials reported no effect of the treatment tested on the risk of dementia or cognitive function. One study, the Syst-Eur trial, reported a beneficial effect of a calcium-channel blocker on the risk of dementia which was halved in the active arm compared with placebo. Because of the relatively small number of incident cases observed (32 overall), the confidence interval (CI) was large, from no effect to a 76% reduction of the risk of dementia, and this finding must therefore be interpreted with caution. In an open follow-up study of the patients in the trial, with a median follow-up of 3.9 years and 64 cases of dementia, the main result was confirmed, and the adjusted relative hazard rate was 0.38 (95% CI, 0.23–0.64). In the PROGRESS trial, although the risk of poststroke dementia was decreased by 34% (95% CI, 3%–55%) in the treatment arm, there was no effect on dementia in the absence of recurrent stroke. In the HYVET (Hypertension in the Very Elderly Trial) study, in which 3336 patients aged ≥80 years with a SBP >160 mm Hg were treated with a combination of diuretic and angiotensin-converting enzyme inhibitor or placebo, the treatment was found to have no effect on the risk of dementia or cognitive decline. All these studies have important limitations: the follow-up is usually short compared with the slow pathophysiological processes leading to dementia, which span over decades; as mentioned for observational studies, there is a lack of biomarkers for dementia and criteria for screening and diagnosis are heterogeneous across studies; most of the patients enrolled in these trials are at low risk for dementia, and there is therefore usually a small number of incident dementia cases, which limits the power to detect any effect. Because of these limitations shared by most trials, the variance in the relation of high BP with brain aging. Structural changes in small brain arteries, as was recently indirectly suggested by findings from the Honolulu Asia Aging Study, increased BP could also lead to functional alterations in the cerebral microcirculation through various mechanisms, as detailed in the second part of this review. SBP and pulse pressure (PP), and mainly central SBP and PP (ie, measured at the level of the thoracic aorta), may exert more deleterious effect on the cerebral microcirculation than diastolic BP, particularly brachial diastolic BP. Indeed, increased aortic stiffness, a major determinant of elevated central SBP, was consistently shown to be associated with increased WML burden, independently of carotid atherosclerosis. This was shown also for carotid stiffness. It is intriguing that among hypertensives the...
prevalence and severity of SVD varies widely. Characteristics of hypertension (duration, variability, control by therapy, associated arterial stiffness, etc.) could at least partly contribute to these differences. Interactions with other non-genetic and genetic factors could also modulate the association of BP with WMLs.66,67

WMLs and other MRI markers of covert VBI could at least partly mediate the relationship between hypertension and brain aging.55 Indeed, there is overwhelming evidence that these markers represent a powerful marker for increased risk of brain aging. Although they are often referred to as asymptomatic, WMLs are associated with subtle neurological deficits, leading to a progressive loss of autonomy.64 Moreover, increasing WML burden is associated with a 2- to 3-fold increased risk of stroke and dementia, as detailed below.43

**WMLs and Risk of Stroke**

A systematic review and meta-analysis of the literature have shown that the presence of extensive WMLs was associated with an increased risk of incident stroke (hazard ratio, 3.5 [95% CI, 2.5–4.9]), both in the general population and in subgroups of individuals with a high vascular risk profile.43 Interestingly, this relationship was still significant after adjusting for hypertension and other risk factors, suggesting that WML better reflects the global impact of lifetime exposure to vascular risk factors, especially hypertension for which WML would represent a cumulative marker of its impact on the brain. Another, less likely explanation would be that other yet unidentified risk factors, for example, genetic factors, are involved in the association between WML and stroke.55,69

Extensive WMLs predispose both to ischemic stroke, especially of the SVD subtype (lacunar stroke), and to intracerebral hemorrhage.70,71

**WMLs and Risk of Cognitive Decline and Dementia**

Extensive WMLs are associated with an increased risk of incident dementia (hazard ratio, 1.9 [95% CI, 1.3–2.8] according to a meta-analysis).43 WMLs seem to be associated mainly with an increased risk of vascular or mixed dementia,43 although some studies also suggest an association with an increased risk of AD.72 WMLs also predict an increased risk of cognitive decline and incident mild cognitive impairment (defined by scoring 1.5 SDs below the sex-specific mean of the distribution for ≥1 cognitive domain).43,69 The strongest associations are observed with decline in global cognitive performance, as well as executive function and processing speed.73,74 Certain regions in the cerebral white matter, such as the anterior thalamic radiation, seem to be more strategic for the occurrence of cognitive deficits.75 Several studies have also suggested a stronger association with cognitive impairment for WMLs located in periventricular versus deep subcortical areas.76–78 One possible explanation for this could be that the periventricular area has a high density of long associating fibers, connecting the cortex with subcortical nuclei and other distant brain territories, whereas the subcortical area contains more short associating fibers that link adjacent gyri.75

Several hypotheses have been raised to explain the mechanisms underlying these associations. A partial interruption of cortico-subcortical neuronal circuits (ie, axonal fibers passing through the white matter that connect the cortex with subcortical structures), because of damage by WMLs could contribute to cognitive decline, especially for tasks involving executive function and processing speed.79 Cerebrovascular lesions could also interact with neurodegenerative lesions of the Alzheimer type, thus accelerating their clinical expression. Indeed, cerebral hypoperfusion may alter clearance of β amyloid, thus favoring amyloid plaque deposition, a key neuropathological feature of AD, whereas β amyloid was shown to be a potent vasoconstrictor, potentially contributing to impaired cerebrovascular regulation.80 In some instances, WML could also be a marker of cerebral amyloid angiopathy, which is highly prevalent in older people, and may contribute to lower performance in specific cognitive domains.81,82

**Other Features of Brain Aging Associated With WMLs**

Importantly, increased WML burden is also associated with a higher prevalence of gait and balance disorders,83,84 depression,85,86 and severe age-related WML independently and strongly predict rapid global functional decline.87 They, therefore, represent a nonspecific precipitating factor of global brain aging.

**Antihypertensive Treatment and WML Progression**

In the 3C-Dijon MRI (Three City-Dijon magnetic resonance imaging) study, which included 1319 elderly individuals who had 2 MRIs at baseline and at 4-year follow-up, SBP change for 4 years was associated with WML volume change.58

In the MRI substudy of the PROGRESS trial performed in 192 patients with a history of stroke, 2 brain MRIs were performed during a 36-month follow-up period. At the time of the second MRI scan, SBP had decreased by a mean of 11.2 mm Hg and diastolic BP had decreased by 4.3 mm Hg in the active arm compared with placebo. The volume of new WMLs was lower in the treatment arm compared with placebo (0.4 versus 2 cm³; \(P=0.047\)). The greatest difference was observed in the group of patients with severe WMLs on the first MRI scan. In this group, no new lesions were observed in the treatment arm of the study, whereas WML volume increased by 7.6 cm³ in the placebo arm of the study (\(P=0.001\)).37 In the PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial, which compared an angiotensin II receptor blocker with placebo in 771 patients, no difference in WML progression was observed between both arms.88 However, mean BP was only 3.0/1.3 mm Hg lower in the active arm compared with placebo.

**Hypertension and Other MRI Markers of Covert VBI**

High BP is also an established risk factor for other MRI markers of covert VBI, that is, covert brain infarcts,44 microbleeds,45 and dilated perivascular spaces (Virchow-Robin spaces).89 Like WMLs, all these features of covert VBI likely reflect cerebral SVD. Putative mechanisms partly overlap with those for WMLs.80 The vast majority of covert brain infarcts are lacunar brain infarcts, that is, of small size (<15–20 mm), and located in deep brain regions. Microbleeds correspond to small collections of hemosiderin-laden macrophages around small perforating vessels. Dilated perivascular spaces represent virtual spaces between the vessel wall of small cerebral
arteries and the brain parenchyma that are filled with interstitial fluid; they may reflect inflammation, increased permeability of the vessel wall, or impaired interstitial fluid drainage.\textsuperscript{89} The latter seems mainly driven by arterial pulse, which is impaired in SVD when arterioles stiffen.\textsuperscript{90} As for WMLs, associations of covert brain infarcts, microbleeds, and dilated perivascular spaces with stroke and dementia risk have also been reported in several studies, described in detail in other reviews.\textsuperscript{44,91–93}

Studies examining the relationship of hypertension with other markers of structural and functional brain aging, such as global and regional brain volumes, are not discussed in this review.

Controversies, Unresolved Questions, and Future Directions

Understanding the Deleterious Effects of Hypertension on the Brain: Future Directions

We summarize here the various mechanisms through which hypertension, viewed from the perspective of accelerated arterial aging, can promote brain damage.\textsuperscript{94}

Blood Pressure Pulsatility in the Cerebral Circulation

An increasing body of evidence suggests that high PP, transmitted into cerebral arteries in response to accelerated aging of large peripheral arteries, can lead to small cerebral artery inward hypertropic remodeling with progressive encroachment of the arterial lumen aimed at protecting the microcirculation from pulsatile stress. By contrast to the resistive function of small arteries, large arteries exert a cushioning function, reducing pulsatility of BP. Arterial stiffness has been identified as the underlying factor for the age-associated increase in SBP\textsuperscript{95} and as a surrogate of arterial aging.\textsuperscript{94} In hypertension, the aorta stiffens in response to the higher BP, thus increasing the velocity of the pressure wave. This, in turn, leads to an early return of the reflected wave, which superimposes to the forward wave and ultimately increases systolic BP whereas diastolic BP is not changed. Thus, pressure pulsatility is increased. The cerebral circulation (together with the kidney) is particularly susceptible to pressure damage, because this is a torrential circulation with minimal vascular resistance, therefore mean and PPs are easily transmitted from the aorta to small cerebral (and renal) arteries.\textsuperscript{64} Recently, several studies have examined the association of arterial pulsatility with VBI. In patients originating from the Oxford Vascular Study and studied within 6 weeks of a transient ischemic attack or minor stroke, blood flow pulsatility index measured with transcranial Doppler in the middle cerebral artery correlated with the extent of WMLs, independent of aortic systolic BP.\textsuperscript{96} In participants in the community-based Age, Gene/Environment Susceptibility–Reykjavik study free from stroke or dementia, carotid flow pulsatility index, as well as carotid PP, and carotid-femoral pulse wave velocity were each associated with an increased risk for covert brain infarcts.\textsuperscript{85} However, flow pulsatility index is an index of resistance, which could be the consequence of numerous subcortical infarcts, rather than an index of pressure pulsatility. Thus, alternative models of the cerebral circulation should be studied, measuring either the input impedance at the entry of the middle cerebral artery or carotid stiffness as proxy for middle-size cerebral artery stiffness. For instance, in 1800 participants from the 3C-Dijon Study, increased carotid stiffness was associated with increasing WML volume, independently of vascular risk factors and carotid plaque.\textsuperscript{63}

Impaired Autoregulation of Cerebral Blood Flow, Hypoperfusion, and Microvascular Ischemia

In hypertension, the inward remodeling of small cerebral artery and associated increased myogenic tone impair vasomotor reactivity, limit the autoregulation of cerebral blood flow, and increase susceptibility to focal ischemia,\textsuperscript{97} when BP is transiently or acutely low. It has been hypothesized that repeated episodes of focal ischemia may lead to white matter damage.\textsuperscript{97} Experimental studies demonstrated that pial arteries, which are essential for optimal neurovascular coupling, that is, regulation of cerebral blood flow according to local neuronal activity and metabolism, are particularly sensitive to the increased pulsatility observed with arterial aging.\textsuperscript{98} The resulting increased myogenic tone and hypertrophic remodeling expose neurons to hypoperfusion in face of even transient acute hypertension.\textsuperscript{99,100} Rothwell et al\textsuperscript{101} demonstrated an increased risk of stroke in patients with exaggerated visit-to-visit variability of SBP and suggested that repeated episodes of hypoperfusion and microvascular ischemia, which are more likely in those patients, could favor tissue damage and stroke. Whether an exaggerated visit-to-visit variability of SBP is also a risk factor for WMLs remains to be established. Similarly, few studies have examined the relationship between BP variability and the risk of dementia and the role of WMLs in this relation.\textsuperscript{102} These considerations also apply to short-term BP variability (ie, within a 24-hour period), which is a well-accepted risk factor for stroke. Because aortic stiffness is a major determinant of SBP, and because it can increase the variability in SBP, it is indeed important to demonstrate whether aortic stiffness can also influence SBP variability. This has been shown in 911 untreated, nondiabetic patients with uncomplicated hypertension,\textsuperscript{103} in whom short-term SBP variability indices were associated with aortic stiffness independently of age and 24-hour SBP. These findings should be strengthened by additional studies, measuring not only short-term variability but also visit-to-visit variability.

Pulse Wave Encephalopathy

Ten years ago, Bateman et al\textsuperscript{104} raised the hypothesis that structural and functional changes of the cerebral circulation in patients with hypertension were caused by an excessive turnover of the cerebrovascular fluid, induced by excessive pressure pulsatility. They named it pulse wave encephalopathy.\textsuperscript{104} As indicated above, the cerebral circulation, characterized by a torrential circulation with minimal vascular resistance, is particularly susceptible to pressure pulsatility.\textsuperscript{64} The transmission is further amplified by the incompressibility of the skull. Thus, small cerebral arteries are particularly exposed to the high-pressure fluctuations that exist in the carotid arteries. Pulse wave encephalopathy is thought to be the mechanism underlying periventricular WMLs, which in contrast to deep subcortical WMLs may not be of ischemic origin. The pulsatile movements of cerebrospinal fluid because of the intracranial PP waves may damage the ependymal lining,\textsuperscript{104,105} and such ependymal alterations were shown to correlate significantly
with periventricular WML burden. All 3 aforementioned mechanisms, high PP in cerebral vessels, impaired autoregulation of cerebral blood flow, and pulse wave encephalopathy, emphasize the central hemodynamic role of aortic stiffness.

A better understanding of the hemodynamic consequences of hypertension on brain damage is mandatory to select not only the most appropriate therapeutic approach but also to optimize prevention, which should be started early in individuals at high risk of developing brain damage. In this regard, aortic stiffness and central PP could be measured in epidemiological studies and randomized clinical trials having cognitive decline, dementia, or WMLs as end points.

Why Is the Evidence of the Relationship Between Hypertension and Cognitive Decline Not Stronger?

As explained above, there is a strong robust association between hypertension and the risk of stroke, which in turn is a strong determinant of dementia. Similarly, the relationship between hypertension and covert VBI is also well demonstrated and these lesions have been related to the deterioration of many cerebral functions. However, the association among hypertension, cerebral dysfunction, and specific cognitive abilities remains elusive. Although compensatory mechanisms and brain reserve could partly contribute to this discrepancy, given the strength of the association of hypertension with VBI and of VBI with cognitive decline, this is unexpected.

Lack of Strong Relationship Does Not Support the Concept of a Broad Prevention Trial

Compared with other target organs, the brain to date has not been the primary research focus of hypertension specialists and BP not a major topic of interest for neurologists specializing in dementia, which explains the relative paucity of data despite the importance of this domain. There are, nevertheless, several observational studies that have studied the consequences of hypertension on the brain but few with a long-term follow-up, which is critical to fully understanding the complexity of this age-modified relationship. If, as suggested by these studies, a high BP measured in midlife is indeed a risk factor for dementia but not when BP is assessed in late-life, prevention of dementia by a BP-lowering drug would not be efficient if initiated in older individuals. A therapeutic trial dedicated to this question would therefore require an intervention in midlife, implying a large sample and a long follow-up, which would make the costs unsustainable.

High-Risk Group Strategy

As pointed out above, the burden of VBI is heterogeneous and only individuals with a high VBI burden are exposed to a subsequent accelerated brain aging, at least during the follow-up periods of available studies compared with those with a lower burden of VBI. It has also been shown that the progression of WMLs is more marked in individuals who already have a high burden of WMLs and that lowering BP is most efficient in this group. Among hypertensive individuals, there may be a group of individuals at high risk of cerebral dysfunction and the grade of WMLs could be a marker of this liability and of the associated risk. If the risk of hypertension-related cerebral dysfunction was indeed limited to a high-risk group, this could explain why no strong global association is observed between hypertension and dementia as the effect of hypertension would be diluted. It therefore seems reasonable to suggest that the next step toward a possible prevention of hypertension-related cerebral aging should be a proof of concept trial on individuals defined by a high burden of VBI. Other high-risk groups could be considered such as individuals with a high risk of cognitive deterioration related to neurodegenerative lesions. Indeed, individuals with a high burden of neurodegenerative lesions may be particularly exposed to accelerated clinical expression of the latter because of VBI. Hence, preventing the occurrence of other neurodegenerative lesions being examined in these individuals.

Figure. Putative pathways linking elevated blood pressure to brain aging.
or progression of VBI through a BP-lowering trial in this high-risk group might prove effective. The identification of high-risk patients could rely on neuroimaging markers reflecting AD pathology, such as Pittsburgh compound B positron emission tomography, or longitudinal clinical markers such as a regular trend of declining performances on cognitive.

Clinic Corner

Should We Screen Patients With Hypertension for Covert VBI?

Given the strong relationship between BP and covert VBI, and given the powerful predictive value of VBI markers for risk of future stroke and dementia, should clinicians screen all patients with hypertension for covert VBI?

Performing systematic brain MRI scans in all patients with hypertension is unrealistic from an economic and practical perspective. Hence, developing screening tools to identify hypertensive individuals with a high prevalence and burden of VBI (high-risk group) could be valuable for prevention strategies. To be acceptable and feasible, these screening tools should involve noninvasive, affordable tests that can be performed easily in large groups of patients and can be monitored longitudinally in a cost-effective way. These could, for instance, include simple quantitative cognitive tests in domains affected by VBI (as a marker of the latter and not as a screening tool for dementia), or specific characteristics or hemodynamic consequences of elevated BP, such as measures of arterial stiffness, although these would need to be formally evaluated.

Regardless of the screening method, detecting covert VBI in patients with hypertension will be relevant only if efficacious prevention strategies can be proposed. At present evidence for these is limited and more studies are needed to demonstrate that it is possible to slow down the progression of VBI and that it will also reduce the risk of stroke and dementia.

What Should a Clinician Do in a Patient With Apparently Asymptomatic VBI on MRI?

As brain MRI has become widely available, clinicians often have to deal with the incidental discovery of covert VBI, especially WMLs. These are highly prevalent in the general population, and in most instances patients should be reassured. Small punctuate subcortical WMLs and thin pencil-like periventricular lining, by far the most frequent, tend to show limited progression.

In patients with multiple silent lacunar infarcts or extensive WMLs (Figure), detailed screening for vascular risk factors and optimized management of the latter should be considered. Indeed, extensive WML is an important risk factor not only for dementia but also for stroke, for which efficient prevention strategies have been validated. Data from randomized trials on the management of covert VBI are scarce, but, as detailed above, they do suggest that more aggressive antihypertensive treatment may be associated with reduced WML progression in patients with a history of stroke, especially in those with the largest WML volume at study entry. Moreover, optimal treatment of hypertension is a central component of primary stroke prevention. Given the strong association observed between elevated daily ambulatory versus office-based BP measurements and WML progression, monitoring the former in patients with extensive VBI could be considered. Data on the management of vascular risk factors other than hypertension in patients with diffuse WMLs or covert brain infarcts are lacking, but again established algorithms for primary stroke prevention could be applied.

Whether patients with extensive covert VBI should be systematically screened for cognitive deficits is a matter of debate. Given the lack of efficient drugs to slow down or prevent conversion to dementia at this time, neuropsychological investigations could be limited to patients with a cognitive complaint. Screening patients with hypertension for cognitive impairment in the absence of extensive VBI is not justified. Overall, clear recommendations are currently lacking for the work-up and management of patients with extensive covert VBI. Open questions include methods for BP monitoring, choice of antihypertensive drugs, criteria for referring patients to a neurologist and performing detailed neuropsychological investigations, and the clinical utility of a follow-up MRI. Experts from professional societies, encompassing the fields of hypertension, cerebrovascular disease, dementia, and brain imaging, should consider establishing a joint consensus statement that could guide healthcare professionals in the management of patients with covert VBI.

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