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SUBCLINICAL BRAIN DAMAGE AND HYPERTENSION

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Hypertension, beyond its well-known effect on the occurrence of clinical stroke, is also associated with the risk of subclinical brain damage noticed on cerebral MRI, in particular in elderly individuals [1, 2]. The most common types of brain lesions are White Matter Hyperintensities (WMH) — which can be seen in almost all elderly individuals with hypertension [1, 2] although with a variable severity (Figure 1) — and silent infarcts, the frequency of which varies between 10% to 30% according to studies (Figure 2) [3].

Both lesions are characterized by high signal on T2-weighted images. Silent infarcts may be singled out by their low signal on T1-weighted images (Figure 2). Another type of lesion, more recently identified, are microbleeds, which are seen in about 5% of individuals and are small, homogeneous, round foci of low signal intensity on MRI Gradient echo (GRE) T2* images. Like WMH and silent infarcts, microbleeds are more frequent in individuals with hypertension.

Hypertension is the main modifiable risk factor for subclinical brain damage. Several studies have suggested that sustained or uncontrolled hypertension is associated with a greater WMH load [2, 4]. The level of blood pressure also seems to play a role — higher blood pressure values being associated with higher grades of WMH [4, 5]. These dose-dependent effects of the duration and level of BP provide strong support for a causal relationship between high BP and WMH, similar to that already reported for stroke.

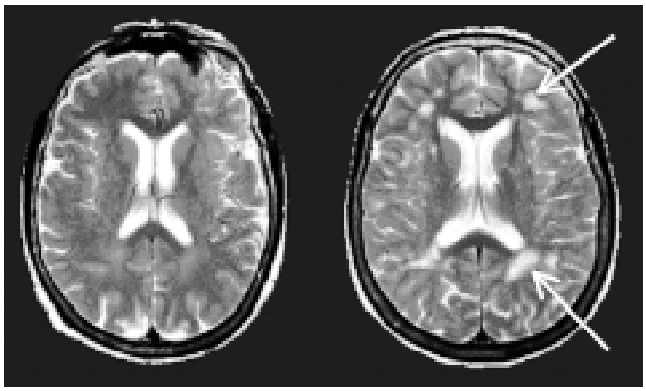

Figure 1. T2-weighted MRI exams of two 65-year-old individuals. The subject on the left has no apparent subclinical brain lesions on this slice whereas the subject on the right has a severe grade of white matter hyperintensities (*arrows*)

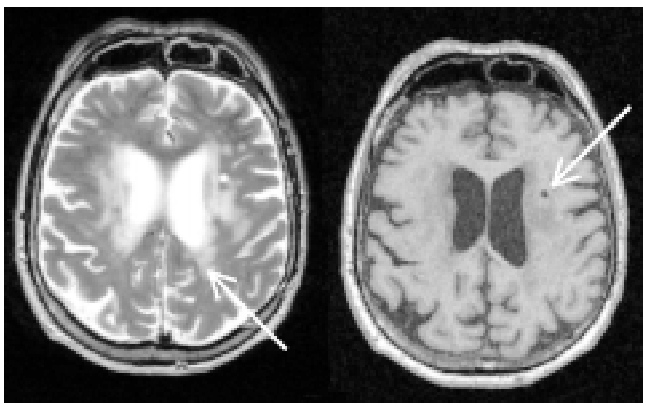

Figure 2. T2-weighted (*on the left*) and T1-weighted (*on the right*) MRI exams of the same subject at 75 years old. This subject has a severe grade of WMH (*arrow*), mainly in the periventricular area, easily seen on the T2 exam (*left*). He also has a silent infarct (*arrow*) in the white matter which appears in hyposignal on the T1-weighted exam (*right*)

Predictive value of subclinical brain damage for cognitive impairment and stroke

At first, these MRI cerebral lesions were considered benign and merely associated with aging. They were even called UBOs — Unidentified Bright Objects! In the past 15 years, several large community-based studies that have included large numbers of individuals with MRI exams have shown that these lesions were not so silent and were associated cross-sectionally with subtle cognitive of motor impairment. It was also recently discovered that they were associated with incident cognitive deterioration or dementia [6], depression [7], and gait disturbances [8].

These associations are probably largely due to the direct consequences of these lesions on the brain circuits and particularly to the disconnection of subcortical-cortical loops. Indeed, small, clinically silent brain infarctions appear to be at least as strong a risk for subsequent dementia [6] as larger, clinically evident strokes. In most cases dementia is not caused by the simple burden of vascular lesions but also by pre-existing neurodegenerative lesions which are very common in the elderly. The occurrence of vascular lesions could simply reveal the ongoing development of Alzheimer's disease in the patient. The interaction between neurodegenerative factors and stroke in the risk of dementia was highlighted in the Nun study [9]. 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 Alzheimer's disease.

Several studies have described WMH or the presence of silent infarct as a predictor of incident stroke in the general population [10, 11] and of stroke recurrence among patients with transient ischaemic attack or stroke history. In such instances, WMH could be considered as the harbinger of further clinical events. In the 3C study, a large population-based cohort study in the elderly in which we performed cerebral MRI in 1924 participants 65 years old and over, we found that those in the highest quartile of WMH had a more than five-fold increased risk of stroke during follow-up compared to those with a WMH load below the median [12]. Interestingly, there was no increased risk of other vascular events, suggesting that WMH was a specific predictor of the risk of stroke.

Systemic arterial damage and subclinical brain damage

The precise mechanisms underlying the development of WMH, silent infarcts, and microbleeds remain unclear. In recent years a large number of studies have reported strong relationships between peripheral artery damage and either subclinical brain damage or cognitive impairment. Alterations of carotid wall thickening, aortic stiffening, and small artery remodelling in patients with cognitive decline have allowed a link to be made between vascular aging and vascular cognitive impairment (VCI), underlining the aggravating role of hypertension.

The relationship between carotid intima–media thickness (IMT) and cognitive function has been analyzed cross-sectionally [13] and longitudinally [14–16] in few studies. Studies differed as far as the study population, the definition of carotid IMT, and the neuropsychological test adopted to evaluate cognition were concerned. Despite this heterogeneity, a significant inverse relationship between carotid IMT and cognitive function was observed in all studies. In other words, the thicker the artery the lower the cognitive performance. This relationship was significant after controlling for age and education; some studies further adjusted for the presence of depressive symptoms [15, 16] and/or level of CV risk factors [15].

Carotid-femoral pulse wave velocity (PWV), the "gold standard" for evaluating arterial stiffness [17], was higher in any group of cognitively impaired subjects — with or without dementia [18]. An inverse relationship between PWV and cognitive performance was reported cross-sectionally [13, 19]. Carotid-femoral PWV was also associated prospectively with cognitive decline before dementia, in studies using a cognitive screening test [20, 21] and more specifically tests of verbal learning and delayed recall, nonverbal memory [21]. These relationships remained significant after controlling for age, gender, education, and blood pressure levels. Other studies reported a significant positive relationship between arterial stiffness and volume or localization of WMH — a known factor predisposing to vascular dementia [22] — on neuroimaging [23, 24].

To our knowledge, no study has investigated the relationship between cognitive decline or WMH, and the remodelling of small arteries harvested from human subcutaneous and omental fat tissue. Retinal arterial

narrowing, assessed non invasively from fundoscopic methodology or scanning laser flowmetry [25, 26], correlates with increased arterial stiffness [25] and cerebral small-vessel disease [26].

Mechanisms relating systemic arterial damage to subclinical brain damage in hypertension

Hypertension is associated with abnormalities of large arteries: mainly increased wall thickness and stiffness, and small arteries: mainly internal remodelling. The pathophysiological association between systemic arterial damage and VCI can be analysed for each type of arterial damage, although the causal link is difficult to determine. Carotid wall thickening, which reflects both atherosclerosis and a higher strain due to hypertension, has been associated with several CV risk factors, including metabolic, inflammatory, and dietary factors, which have also been associated with cognitive decline [14, 27]. An increased aortic stiffness, in response to high blood pressure levels loading the stiff components of the arterial wall, may be related to microvascular brain damage through several mechanisms: (a) endothelial dysfunction and oxidative stress [28], (b) a mutually reinforcing remodelling of large and small vessels (i.e. large/small artery cross talk) [29], and (c) exposure of small vessels to the high-pressure fluctuations of the cerebral circulation [30], which is passively perfused at high-volume flow throughout systole and diastole, with very low vascular resistance. Internal remodelling of small arteries, which is accelerated by hypertension, ultimately leads to occlusion of end arterioles. Finally, WMH and silent infarcts are considered to be markers of chronic cerebral ischaemia resulting from damage to small cerebral vessels.

Prevention of subclinical brain damage by antihypertensive drugs

WMH and other subclinical brain lesions are involved in the occurrence of major neurological disorders and appear to cause accelerated aging of the brain. Trying to control their aggravation is therefore an important goal. As hypertension is their major modifiable risk factor it seems logical to test first the hypothesis that a blood pressure lowering treatment may modify their evolution.

This question was addressed in a clinical trial, the PROGRESS MRI study [22], a sub-study of the PROGRESS trial. In this sub-study, 192 patients were enrolled (mean age of 60 years), 89 of whom were in the active treatment arm of the study, the other 103 patients being assigned to the placebo arm. Each participant underwent an initial brain MRI at the start of the study and a second MRI examination after a mean follow-up period of 36 months. The variability between the two examinations due to technical aspects (position of the head in the scanner, sections of different sizes taken in different positions) was limited by using image analysis techniques to realign the images and for automatic segmentation after the recording of scans in an object-oriented database. These techniques rendered the images as comparable as possible, and an independent observer blind to the clinical data and order of examinations was then able to compare the scans in detail, detecting and measuring each new lesion. A neurologist analyzed the initial scan results and identified 13% of the patients as having moderate WMH and 19% as having severe WMH. At the time of the second MRI scan, SBP had decreased by a mean of 11.2 mm Hg and DBP by 4.3 mm Hg. The overall risk of a new WMH lesion was 43% lower in the treatment arm than in the placebo arm of the study, although this difference was not statistically significant ($p = 0.10$) [22]. The volume of new WMH lesions in the treatment arm was only one-fifth of that in the placebo arm of the study (0.4 cm^3 versus 2 cm^3; $p = 0.047$). The greatest difference was observed in the group of patients with severe WMH on the first MRI scan. In this group, no new lesions were observed in the treatment arm of the study, whereas the volume of WMH increased by 7.6 cm^3 in the placebo arm of the study ($p = 0.001$) [22]. This group also displayed the most marked progression of WMH over the four-year follow-up period, thus confirming the results of several observation studies. Finally, it was recently shown in the PROGRESS trial that patients with a high load of WMH lesions had a 7.7-times higher risk of severe cognitive deterioration or dementia (95% CI = 2.1–28.6).

These preliminary results are encouraging because they show, for the first time, that it is possible to decrease the development of WMH by lowering arterial blood pressure. However, given the relatively small number of patients studied, these results cannot be considered as conclusive. They require confirmation (or negation) in larger groups of patients. Furthermore, all the patients in the PROGRESS study had a history of stroke, limiting the extent to which these results can be generalized.

Ideally, the next step would be a trial in patients with moderate to severe WMH grades. There is now strong evidence that this group is exposed to a rapid increase in WMH volume but also to an immediate risk of severe cognitive deterioration and dementia. As WMH has been shown to play a role in the occurrence or aggravation of cognitive decline and dementia, limiting their progression may be the cornerstone in a wider strategy to prevent dementia by controlling vascular factors.

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