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). A 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.

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 UBDs — Unidentified Bright Objects! In the past 15 years, several large community-based studies 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.

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 factor as larger ones [6] and, because there are many of them, they are 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 infarcts as a predictor of incident stroke in the general population [10, 11] and of stroke recurrence among patients with transient ischemic 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 of age 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 arterial disease, age and either subclinical brain damage or cognitive impairment. Alterations of carotid wall thickening, aortic stiffening, and small artery remodeling in patients with cognitive decline have allowed a link to be made between vascular aging and WMH, 

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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 WMH 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 dyslipidaemic 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 arteries. 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 [31]. 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-processing 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 then able to count 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 was decreased by a mean of 11 mm Hg and DBP by 4 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-sixth of the size of the stroke (0.4 cm³ versus 2 cm³; 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 cm³ 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 history of 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 of 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.

References

23. Kearney-Schwartz A, Rossignol P, Bracard S, et al. Cerebral vascular function and increased arterial stiffness, limiting their progression may be the cornerstone in a wider strategy to prevent dementia by controlling vascular factors.