Blood Pressure and White Matter Hyperintensity Volume – A Review of the Relationship and Implications for Stroke Prediction and Prevention

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Abstract

A heavy burden of white matter hyperintensities (WMH) is a risk factor for stroke and vascular cognitive impairment making it important to understand their pathophysiology, aetiology and clinical implications. Ageing studies suggest a linear relationship between blood pressure (BP) and both WMH and microstructural integrity in normal-appearing white matter and, after age, hypertension is the strongest risk factor for WMH. Numerous large population-based observational studies have reported significant associations between elevated BP and WMH burden, however, the relative importance of systolic versus diastolic BP remains controversial. Limitations of prior studies include the use of only a single measurement of BP and oversimplifying hypertension as a dichotomous variable. Race/ethnic differences in the association between BP and WMH have been suggested, but most studies only included older Caucasians. Antihypertensive treatment has been demonstrated to slow WMH progression, but lowering BP in the elderly may also reduce brain perfusion in those with poor autoregulation. Ongoing trials aim to clarify the effects of BP treatment on WMH progression in multi-ethnic populations and the implications of these findings for stroke prevention require further study.

Keywords

Leukoaraiosis, vascular cognitive impairment, blood pressure, hypertension, cerebral small vessel disease, white matter hyperintensities

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With the ever-increasing availability and clinical use of brain magnetic resonance imaging (MRI), the frequency of white matter hyperintensities (WMH) has become more readily apparent. As a heavy burden of WMH has been shown to be an important risk factor for incident stroke as well as vascular cognitive impairment,[1] it is important to understand the pathophysiology, aetiology and clinical implications of WMH volume. Evidence suggests that hypertension is the strongest modifiable risk factor for WMH[2–8] and raises the possibility of both prevention and treatment strategies, but clinical trials are lacking and further studies are needed.

Neuroimaging

WMH are demonstrated on T2-weighted MRI sequences. These damaged regions are evidenced on the T2 sequence as high signal intensity, which appear bright.[9] They are considered white matter lesions if hyperintense on T2-weighted, fluid-attenuated inversion recovery and proton density images, without prominent hypointensity on T1-weighted images.[1] They indicate areas of increased brain water content in white matter tissue, but the degree of damage to axons and supporting cells is not clear and remains an area under study (see Pathology section below).[9] Recent evidence using diffusion tensor imaging has suggested a linear relationship between blood pressure levels and the microstructural integrity of both normal-appearing white matter and white matter hyperintensities. In hypertensive patients, the microstructural integrity of the cerebral white matter is significantly more affected than in normotensive patients.[10]

Pathology of White Matter Hyperintensities

The most common areas affected by WMH are in the deep white matter of the cerebral hemispheres, especially in the distribution of end-arteries and arterioles that supply a border-zone territory with minimal irrigation by collateral vessels. In areas identified as hyperintensities on MRI, pathological studies have reported myelin pallor, loss of tissue density, myelin and axonal loss, and gliosis.[11,12] These lesions are hypothesised to be caused by chronic hypoperfusion of the white matter due to low-grade vascular insufficiency resulting in ischaemia,[12] and are often associated with structural changes of the vessels, including hyalinisation, tortuosity, elongation and narrowing with arteriosclerosis and lipohyalinosis.[12,13] Many of these changes have been associated with hypertension.[14]

Aside from ischaemia, another hypothesis is that chronic hypertension results in disruption of the blood–brain barrier (BBB), allowing toxic plasma constituents as well as destructive enzymes to leak into the white matter.[15] Similar to the changes thought to cause ischaemia, breakdown of the BBB may also result from hypertensive damage causing lipohyalinosis and luminal narrowing of the small perforating arteries and arterioles that irrigate the white matter, and

therefore cerebral arteriosclerosis.[16] A number of inflammatory markers associated with an increased risk of stroke have been identified, including C-reactive protein and lipoprotein phospholipase A2 and there is some evidence that relative elevations of these markers are seen in those with extensive WMH.[17] Venous collagenosis is also a proposed mechanism for white matter lesions. Deposition of collagen fibres in the periventricular venules may cause narrowing of the venular lumen and disruption of the BBB at the venular level, and in turn increase perfusion pressure on the arterial side of the capillary bed leading to WMH formation.[12,18] Finally, cerebral amyloid angiopathy has been associated with WMH, especially in patients with Alzheimer's disease and is felt to result from deposition of amyloid in the *tunica media* and *adventitia* of white matter vessels.[12]

Epidemiology

Population-based studies on the prevalence of WMH in adults has ranged from 11–21 % for those in their sixties to 94 % at 82 years of age.[19,20] Known modifiable risk factors for white matter disease include hypertension, diabetes, dyslipidemia, smoking and obesity.[1,2,19,21,22] Apart from age, hypertension is the most common and strongest risk factor for WMH, as evidenced by several epidemiological studies, both cross-sectional and longitudinal.[2–8] Although estimates of hypertension prevalence vary, based on the National health and nutrition examination survey (NHANES) in 1991–1994, the age-adjusted hypertension prevalence was 25 % and in 1999–2002 was 28.6 %,[23] however, the prevalence is much greater in those with a heavy burden of WMH.

In the current literature, there are seven notable population-based observational studies on the relationship between blood pressure and WMH burden, four of which were cross-sectional and three of which were longitudinal. All seven studies showed a significant association between elevated blood pressure and WMH burden, although methodologies and sample sizes varied across the studies, including the way WMH were measured and quantified. All seven studies utilised measured blood pressure levels rather than relying on self-reported hypertension. However, a limitation in the current literature is that most studies used a single measurement of blood pressure and therefore were not able to capture changes in blood pressure over time. Further, most studies examined hypertension as a dichotomous variable rather than examining blood pressure continuously that would have allowed for evaluation of a dose-response, and the majority of studies were conducted in homogeneous, predominantly Caucasian, older populations that limit generalisability to other populations.

In the Cardiovascular health study, 3,301 stroke-free participants over the age of 65 who had undergone MRI were evaluated. WMH burden was positively associated with systolic blood pressure, diastolic blood pressure and orthostatic hypotension, and the relationship was similar regardless of whether the WMH were more predominant in the periventricular, subcortical or both regions.[3] The Framingham Heart study also evaluated 1,814 patients who were stroke-free as well as dementia-free and found that the Framingham Stroke Risk Profile and its component risk factors including hypertension were strongly associated with WMH volume.[7] In this cohort, hypertension was associated with a 70 % increase in the odds of having a large WMH volume. This study was one of the first to use quantitative MRI measures of WMH rather than semi-quantitative visual ratings. The Epidemiology of Vascular Aging (EVA)-MRI cohort, in which 845 elderly patients underwent brain MRI four years after study entry, showed that baseline hypertension was associated with a greater than two-fold increase in the odds of having severe white matter lesions at follow-up.[24]

In the Rotterdam study, the prevalence of white matter lesions and their relation to cardiovascular risk factors was studied in a random sample of 111 subjects from the general population age 65 to 84. Twenty-seven percent of subjects demonstrated WMH on MRI. They found that both blood pressure level and hypertension status were associated with the prevalence and severity of white matter lesions, but only among those aged 65 to 74, a younger subset of their cohort.[2]

There have also been studies that addressed the duration of elevated blood pressure and its association to WML severity. In particular, midlife blood pressures have been found to be associated with a greater WMH burden. The Rotterdam scan study prospectively addressed the relationship of duration of hypertension and WMH and reported that a 20-year duration of hypertension increased the risk of white matter lesions about 20 fold, especially among middle-aged individuals.[25] The Honolulu Asia aging study (HAAS) found that variations in SBP in midlife may also be a contributing factor to the development of WMH.[26]

The severity of white matter disease has been shown to be directly related to blood pressure, but the relative importance of systolic versus diastolic blood pressures remains controversial.[27,28] Although some studies have demonstrated the importance of systolic blood pressure in WMH aetiology,[7] a subset of studies has suggested that a higher baseline diastolic, more than systolic, blood pressure is associated with WML progression. The mechanisms by which WMH damage occurs is not clear and systolic versus diastolic blood pressures may have different effects on the white matter. High diastolic blood pressure (DBP) is indicative of elevated peripheral resistance, which may reflect small vessel disease, whereas systolic blood pressure (SBP) may be more related to large artery stiffness.[29,30] The arterial borderzone in the periventricular white matter is irrigated by small perforating arteries and arterioles with minimal collateral supply and would implicate DBP in the production of WMH due to small vessel damage or venous collagenosis as noted above. The Prospective population study of women in Gothenburg (PPSW) found that higher middle- and late-life DBP and mean arterial pressure, but not SBP and pulse pressure, were associated with a greater frequency and severity of WMLs in a population based sample followed for 32 years.[28] This study was limited however as it only included female subjects, and computed tomography, rather than MRI, was the imaging modality utilised to detect WMH.

In the Northern Manhattan study (NOMAS), longitudinal BP measurements were examined as correlates of WMH volume in a population that included blacks and Hispanics in addition to whites (n=1,290). This study demonstrated that baseline DBP and longitudinal increases in DBP were independently associated with greater WMH volume, and the association between DBP and WMH volume was greater among blacks and Hispanics compared to whites. In this study, systolic blood pressure was not associated with WMH burden.[27] These findings demonstrate the need for additional prospective data on hypertension and WMH progression in racially and ethnically diverse populations.

Effects of Anti-hypertensives on White Matter Hyperintensities

Studies examining the effects of antihypertensive medication use have also provided insights into the role of hypertension and its treatment in the aetiology and prevention of WMH burden. Antihypertensive medications may slow the progression of white matter lesions over time, as subjects taking antihypertensive medications with better blood pressure control have been shown to have a lower WMH burden than those with uncontrolled blood pressure.[8,24,31]

Studies have also addressed the progression of WMLs over time as related to blood pressure change. In the longitudinal population-based Three-city (3C) Dijon MRI study, 1,319 elderly patients underwent two MRI's four years apart. Progression of white matter lesions, in the periventricular region and in all regions combined, was predicted by baseline diastolic blood pressure, but the association with baseline systolic blood pressure was not statistically significant. In addition, increases in both systolic and diastolic blood pressure were positively associated with progression of white matter lesions over time. Progression in white matter lesions was reduced among those with untreated elevated systolic blood pressure at baseline who were subsequently treated with antihypertensive medications within two years.[31]

The Atherosclerosis risk in communities (ARIC) study also evaluated WMH progression over 10 years in relation to blood pressure changes (n=1,920) and includes both black and white participants. This study demonstrated that cumulative systolic blood pressure was a strong predictor of WMH progression, and stronger than systolic blood pressure measured at any individual time point. This association was similar in both the black and white subjects. Interestingly, in the black subjects only, earlier (midlife) SBP measurements were stronger predictors of WMH progression than later measurements.[32]

Clinical Trials

To date, the only randomised controlled trial addressing blood pressure and WMH is the French MRI sub-study of the Perindopril protection against recurrent stroke study (PROGRESS) clinical trial. In this trial, hypertensive and normotensive patients with a history of stroke were randomised to treatment with placebo or a thiazide/angiotensin-converting-enzyme inhibitor (ACEI) combination as an adjunct to their prior blood pressure regimen. The patients underwent baseline and follow-up MRI at three years in order to compare the progression of WMLs. The results demonstrated that the diuretic/ACEI combination slowed the progression of WMLs in this population. The risk of new WMH was reduced by 43 % in the active treatment group compared with the placebo group. The subgroup of patients most affected were those with severe white matter disease at study entry.[8] This study was not only limited by small sample size (n=192) and the fact that it only included patients with prior stroke, but it only included a highly selected group with minimal racial and ethnic diversity.

In the future, further trials are needed to better understand the effects of blood pressure, diastolic as well as systolic, on progression of white matter disease in multi-ethnic populations. At this time, the ongoing National Institutes of Health (NIH)-funded, Systolic blood pressure intervention trial (SPRINT) is addressing this question. Patients are randomized to the currently recommended target SBP goal of <140 mmHg versus an SBP of <120 mmHg. The primary hypothesis is that cardiovascular disease, including white matter lesions, will be lower in the intensive arm with SBP <120. The results of this trial will provide a high level of evidence regarding the importance of blood pressure lowering in the development of new WMH. Concurrent cognitive evaluations will also show if such reductions are associated with cognitive changes that provide a target for reducing the incidence of vascular cognitive impairment.

Implications for Stroke Prediction and Prevention

A recent meta-analysis showed that WMH are a risk factor for incident stroke.[1] Based on increasing evidence, some of which is presented above, blood pressure is increasingly recognized as perhaps the most important modifiable risk factor for the development of WMH. However, the relationship is complex and the role of blood pressure in the process requires further study. For example, further studies are needed to understand the relative importance of high blood pressures as a cause of WMH through small vessel damage that leads to ischemic demyelination versus breakdown of the BBB associated with inflammation. The role of damage to the venous system also requires additional study. Further, while a number of studies have found an elevated risk of incident stroke among those with WMH in both the general and high-risk populations, the threshold above which the volume of WMH becomes a potent risk factor is not clear. Indeed, many older individuals have WMH as incidental findings on brain scans and clinicians are currently unable to provide advice regarding the risk associated with different amounts of WMH. This is further complicated by the heterogeneous etiology of WMH lesions and the fact that not all WMH are due to vascular damage as noted above, limiting the ability to give specific advice about effective treatments. Data showing that some inflammatory markers are associated with a greater burden of WMH may provide an opportunity to risk stratify patients based on the volume and location of WMH as well as the relative levels of specific markers and further studies in this area are warranted. ■

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