Cardiovascular risk factors, white matter abnormalities and diffusion tensor magnetic resonance imaging

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The growing body of research based on diffusion tensor imaging (DTI) substantiates the utility of these imaging methods in detecting patterns of sparing and involvement of regional white matter (WM) microstructural integrity in normal populations and in diverse neuropsychiatric conditions. Many of these conditions are characterized by changes in brain structural integrity that are subtle on the macrostructural level, but more reliably detectable on the microstructural level.

Today, DTI appears to be a powerful tool and sensitive indicator of WM tissue ultrastructure and damage that utilizes two principal parameters: FA (fractional anisotropy) and MD (mean diffusivity). Fractional anisotropy is a measure of the directionality of diffusion of molecules of water and provides information on WM tract integrity, whereas the mean diffusivity measures the extent of diffusion and is sensitive to ultrastructural damage.

The target of DTI MRI is microstructure. Its use may afford insight into neural mechanisms, regional patterns and the course of WM and cell degeneration as affected by various cardiovascular risk factors, normal aging process, and neurodegenerative diseases.

Among the risk factors, hypertension and obesity play significant roles in development of vascular disease. Hypertension is the most important risk factor for stroke [1] and the major risk factor associated with increased risk of cognitive decline [2] and dementia [3]. Obesity also is related to a higher risk of cognitive impairment [4].

In the community population, hypertension is found to be the major risk factor for asymptomatic WM hyperintensities (WMHs) that are associated with cognitive impairment [5], particularly executive dysfunction and psychomotor speed [6,7]. White matter hyperintensities are areas of increased signal intensity that become apparent particularly on T2 weighted MRI scans. Many studies have demonstrated that the prevalence of white matter hyperintensities is indeed increased in hypertension and a sub-study from the PROGRESS trial has shown that anti-hypertensive treatment actually reduced the progression of WM hyperintensities [8].

The hypothetical explanation of WMHs suggests that the perforating cerebral arterioles supplying WM become susceptible to hypertensive damage, causing WMHs and leukoaraiosis (see below) and, if affected to a larger degree, lacunar strokes. Another plausible mechanism implicates small artery wall remodeling that damages the endothelial cells and cause the leakage of plasma elements into the vessel wall and surrounding brain tissue, contributing to the hypertension-induced WM damage [9]. In addition, reduced cerebral blood flow and reactivity in affected WM may make these areas more prone to transient ischemia-inducing myelin rarefaction [10] and even high-normal blood pressure is associated with increased WMH burden [11]. On the same note, leukoaraiosis – which refers to WM rarefaction and WM disturbances observed as a hypodensity in computed tomography and hyperintensity in a T2-weighted magnetic resonance image – is a result of chronic ischemia, due to damage in penetrating arteries supplying the WM.

Both in normal aging [12] and cerebral small vessel disease (SVD)[13], investigators observed decreased i FA and increased mean diffusivity. However, to date it remains unclear to what extent these morphological alterations in cerebral WM are influenced by cerebrovascular risk factors.

Some authors suggested, for instance, that age-related increase in vascular risk factors is associated with changes in cerebral circulation that produce up-regulation of the arterial blood pressure and chronic hypertension subsequently [14]. Reduction in WM volume has been described even with the milder forms of hypertension [15]. Also, hypertension has been linked to increase in overall WM hyperintensity (WMH ) burden, and in hypertensive adults, decline in posterior cerebral WM has been noted as well [16].

In one recent DTI MRI study [17], the authors examined the effect of hypertension on regional WM in 64 adults above the age of 42 years. In the model, the nine FA regions of interest (ROIs) served as a dependent repeated-measures variable, and age, sex, hypertension status and their interactions as predictors. Whereas uncomplicated aging is associated with significant decrements to WM integrity in anterior regions, univariate post hoc analyses revealed that the hypertension × age interaction was significant only for the occipital and temporal WM FA: F(1,56)=16.87, p<0.01 and F(1,56)=5.60, p=0.02, with a trend observed for the genu of the internal capsule: F(1,56)=3.38, p=0.07.

In other words, vascular risk may underlie the expansion of the age-related deterioration into the posterior areas. Also, the finding that a longer duration of hypertension is related to a greater deterioration in those regions is in accord with that hypothesis. In contrast, in normotensive adults, elevated pulse pressure (and, by inference, increased arterial stiffness) exacerbates the effects of age in the anterior regions.

An important implication of this study is that, independent of aging, a known vascular risk factor such as hypertension emerged as a significant negative modifier of WM aging; even in normotensive individuals higher pulse pressure was associated with decreased anisotropy and increased diffusivity. Their findings also show that even relatively low doses of vascular risk may be sufficient to exacerbate the impact of age on the cerebral WM.

In the older adults who were not screened for vascular disease, hypertension was linked to increase in WM diffusivity within frontal regions [18] or across the cerebral hemispheres.
[19], whereas significant cerebrovascular disease is accompanied by even greater and more widespread increase in diffusivity and decline in FA [18, 19]. Untreated hypertension was linked to lower global FA than treated hypertension in a small sample of elderly patients [20], and compromised anisotropy in the occipital WM was noted in hypertensive individuals compared to normotensive controls [21].

In samples composed of older participants, most of whom were hypertensive, age-related declines in FA were associated with WM loss and increase in WMHs in the same locations [22]. Such findings therefore suggest that increase in severity of vascular disease is associated with proportionately greater declines in WM integrity. However, the authors’ findings show that even relatively low doses of vascular risk may be sufficient to exacerbate the impact of age on the cerebral WM.

Together with the study of Huang and colleagues [21], the above results indicate that hypertension-related microstructural damage to WM is not only apparent in areas with overt leukoaraiosis [e.g., WM hyperintensities; 23; 24; 22], but it also occurs (and probably at an earlier stage) at a level undetectable in imaging modalities that are insensitive to diffusion properties of normal-appearing WM [25].

The damage inflicted by persistent hypertension may result in an expansion of an observed, predominantly anterior pattern of normal aging [25; 26; 27; 28] into more posterior cerebral regions. The same authors [17] reported selective effects of hypertension on WM integrity in temporal and occipital WM, the same regions that have shown similar effect in volume loss [30], and WMH accumulation [23]. Furthermore, they have previously found longitudinal progression of WMHs isolated to parietal and occipital regions, and primary visual cortex shrinkage selective to those with vascular risk, and noted an association of increasing blood pressure with increase in deep (but not periventricular) WMH burden [31].

Notably, taken together these findings make clear that vascular health, not age, affects further accumulation of WMHs, suggesting a pathological rather than normal aging cause [31]. The results reported in this study [17] supported the likelihood of hypertension and vascular risk as the precursor of WM damage proliferation into the posterior areas of the brain that are relatively spared in healthy aging.

A common assumption is that age and cardiovascular disease result in decrease in anisotropy and increase in diffusivity; however, selective loss of WM fibers with uniform orientation from the tissue sample of crossing fibers can result in increased anisotropy and increased or decreased diffusivity as well [31]. Therefore, our current understanding of the underlying regional architecture can guide our interpretation in future studies using DTI MRI [32; 31]. Other likely influences on DTI measures include increased interstitial cerebrospinal fluid (CSF) in WM (e.g., leukoaraiosis) and partial volume effects (PVE) from inclusion of gray matter and/or CSF in the WM sample. Taken together, evaluation of rigorously controlled regional anisotropy values for regional anatomy and partial volume effects (PVE), in subjects known with vascular risk factors, may warrant further investigation.

REFERENCES: