White Matter Hyperintensities: Pearls and Pitfalls in Interpretation of MRI Abnormalities
To the Editor:

Atwood et al acknowledge that the pathophysiology of white matter hyperintensities (WMH) is uncertain and underscore the possibility of ischemic etiology, especially in the elderly. These authors regard WMH as an excellent marker of brain aging and emphasize their heritability in patients with negative correlation with cerebrovascular brain injury.

WMH are neither age-specific nor generally heritable, having been found in both sexes in hypertensive encephalopathy, periperal eclampsia, migraine, and therapy with cyclosporin, interferon-α, and tacrolimus. Kruit and coworkers found WMH in MRI only in women migraine patients, which likely reflects an investigational artifact. Atwood et al did not exclude hypertensive and migraine patients from their analysis, which prominently confounds their interpretation of WMH as indicative of brain aging.

An important pathophysiological clue to the nature of WMH is the characteristic difference in the distribution of infarcts and deep WMH in migraine patients. Predominantly posterior circulation territory (PCT) migrainous infarcts in contrast to anterior circulation infarcts in embolic or atherosclerotic thrombotic strokes in general are likely related to rheological factors. Anatomical vulnerability of the posterior cerebral artery renders it particularly susceptible to vasospastic influences in migraine patients. The rare occurrence of neuroanatomically nonlateralizing—in relation to headache or aura—PCT infarcts renders it particularly susceptible to vasospastic influences in migraine patients. The case of ischemic etiology, especially in the elderly.

Diffuse nonlateralizing distribution of deep WMH unaffected by triptan use indicates that WMH do not reflect the outcome of vasospastic ischemia. Also, local changes during migraine attacks, eg, excessive neuronal activation or excitotoxicity, should logically manifest lateralizing WMH. Deep WMH, in contrast to infarcts, likely resolve totally along with resolution of symptoms and signs after treatment of hypertension or withdrawal (or reduction of dose) of immunosuppressive agents. Vasogenic cerebral edema probably underlies WMH in hypertensive encephalopathy; breakdown of the blood–brain barrier has been shown in human and in rat models. Attack-related, inconsistently-lateralized, and prolonged (>48 hours) hyperperfusion prevails in the cerebral cortex, thalamus, and basal ganglia in migraine.

In direct contrast to infarcts, WMH probably result from intense but self-limited cerebral hyperperfusion. I propose that WMH are markers of transient breakdown of the blood–brain barrier rather than aging.

The heritability of WMH volumes is an intriguing feature. The decline in heritability estimates after age 60 indicates the nongenetic nature of this observation. Another indicator of the nongenetic nature of WMH is the absence of correlation with aging in women despite higher heritability. Migraine is more prevalent in women than in men, from approximately age 14. Breakdown of the aging-marker hypothesis for WMH in women may relate to migraine headaches. Finally, heritability of WMH may relate more to heritability of hypertension or migraine or both. In the absence of any link to cerebrovascular disease, the menopause probably has no independent bearing on WMH. Spontaneous resolution likely underlies significantly smaller WMH volumes at younger age, especially in women, in which cohort the highest prevalence of migraine can be expected. These authors also hope to establish a genetic link between WMH and silent brain infarctions. Unless the resolution or otherwise of WMH is established prospectively, it is premature to link this MRI finding with cerebrovascular ischemic disease. Cross-sectional studies of WMH cannot establish vascular-related genetic influences, as has been suggested. Assumption of the genetic model for WMH is probably incorrect.

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