The Origin of White Matter Lesions
A Further Piece to the Puzzle

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See related article, p 1037.

Incidental areas of high signal intensity on T2-weighted MRI of older individuals termed white matter hyperintensities or white matter lesions (WML) have sparked scientific and clinical interest over the past 25 years. Extensive research has provided compelling evidence that at least more extensive forms of WMLs are a consequence of and indicative for small vessel disease, and thus are associated with a higher risk for stroke, dementia, and mortality. Furthermore, the longitudinal Leukoaraisis And Disability (LADIS) study confirmed that severe WML strongly predict global functional decline in general beyond individual associations of WML extent with cognitive functioning as well as gait, balance, and mood disorders. Similar data come from several other cohorts. The exact mechanism(s) of WML formation, however, are still much less clear.

In this issue of the Journal, de Groot et al report on a very elegant study which provides convincing evidence for the gradual development of WMLs both regarding the formation of new WMLs and also their expansion and growth over time. Using diffusion tensor imaging and the fluid-attenuated inversion recovery sequence, they searched for subtle changes that might have preceded new or enlarging WMLs in a large older cohort recruited among the general population of Rotterdam. Baseline and follow-up MRI examinations had been done 3.5 years apart using the same 1.5 Tesla MR-scanner and imaging sequences. Given the complexity of the analysis of diffusion tensor images and the errors that might be introduced by incorrect coregistration, they chose 3 different approaches to strengthen their findings. These consisted of a whole brain analysis, of regional matching, and a test for voxelwise differences. All these analyses showed that low fractional anisotropy, high mean diffusivity, and relatively high fluid-attenuated inversion recovery intensity at baseline preceded WML development during follow up. This was true both for normal appearing white matter (NAWM) giving rise to new WML formation as well as for areas in which existing WML had just expanded. This work, thus, provides quite solid evidence for an overall gradual development of WMLs.

The authors in their conclusion also stress the fact that visually appreciable WMLs obviously are only the tip of the iceberg of white matter pathology.

Provided insights are very important but not completely new. Changes in the composition of NAWM which increase with the severity of WMLs have already been shown earlier using magnetic transfer and diffusion tensor imaging and voxelwise coregistration of diffusion tensor imaging data also indicated that these abnormalities increase toward the proximity of WML. However, recognition of small vessel disease-related white matter damage as a diffuse rather than a very focal process appears crucial not only in understanding its pathophysiology but especially in terms of clinical correlations. Given that NAWM constitutes the, by far, largest portion of white matter in the brain in most individuals, even with severe WML, it is likely that even minor NAWM damage may have more impact on cerebral functioning than WMLs per se. Support for this assumption comes from studies which demonstrate a closer correlation between diffusion weighted imaging metrics of the NAWM with cognitive dysfunction than with WML volume. In this regard, it is reassuring that WML severity also appears to be a good indicator for even the invisible white matter damage.

The findings of de Groot et al that diffusion tensor imaging metrics and fluid-attenuated inversion recovery signal intensity independently associate with WML development attest to the rather complex mechanisms involved in their pathophysiology which likely entail primary and secondary changes in the brain. Changes in vessel wall permeability and diffuse disruption of the blood–brain barrier leading to water accumulation in the interstitial space and secondary demyelination, hypoperfusion attributable to altered cerebrovascular autoregulation, fluid shift from the ventricles through impaired ependymal lining, and axonal disruption have been discussed among others.

There are also some limitations to the conclusions and findings of de Groot et al. First, although a gradual development is obviously the likely mechanism for the majority of WML, there is also accumulating evidence that even small acute infarcts may turn into WML. Second, despite the technical sophistication in their work, it appears still difficult to define the threshold above which an area of NAWM will start to turn into a WML. Such insight could also serve to define individuals who are likely to suffer from WML progression. Third, we unfortunately do not yet know the speed with which the abnormalities described in the NAWM develop. Fourth, these subjects were not particularly old (mean 67±5 years), and the trajectory of pathological changes in the brain in the seventh decade may not be the same as in the eighth or ninth decades. We do not know much about the influence of nonimaging variables, such as hypertension or smoking, on the brain tissue parameters, although we
know from other studies that hypertension is associated with altered mean diffusivity in otherwise healthy men of similar age to the patients in the de Groot et al study,\textsuperscript{10} as well as in much younger subjects,\textsuperscript{20} suggesting altered water content. Finally, the coassociation between advancing age, changing mean diffusivity, fractional anisotropy, and advancing white matter hyperintensity on fluid-attenuated inversion recovery should not be overlooked, aging being one of the, if not the strongest, risk factors for all these imaging variables and WML. Although we, thus, have come a step further in our understanding of WML pathophysiology, it may still take some time before we will get a real handle on it.

**Disclosures**

Dr Wardlaw holds academic grants from government and charitable funding agencies, some of which are relevant to this topic.

**References**

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