The increasing application of neuroimaging techniques has led to the frequent discovery of cerebral white matter lesions, referred to as white matter hyperintensities (WMHs) in this article, which appear as hypodense areas on computed tomography (CT) scans or as hyperintense regions on T2-weighted and fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) sequences. Since their discovery, almost every aspect of WMHs has been surrounded by controversy. Despite the abundant literature on this subject, relatively little progress has been made in determining the etiology, pathology, or even the clinical significance of these lesions.

The prevalence of WMHs in asymptomatic healthy subjects varies widely depending on the technique used for their identification, the type of lesion examined, and the characteristics of the population studied. Large-scale population-based studies have shown that prevalence rates range from 27 to 96%. However, prevalence rates are generally higher in patients with dementia, and have been found to differ among ethnic groups and with gender.

Many risk factors have been associated with the frequency and severity of WMHs, but the strongest and most consistently reported is increasing age. Hypertension is the next most important risk factor, with a recent study demonstrating a reduced risk for increased WMH volume over two years in subjects with successfully treated hypertension; however, there is some debate over whether systolic or diastolic blood pressure (BP) is significant. Some studies observed that both systolic and diastolic BP were higher in subjects with WMHs, while others found that mean systolic BP was significantly higher in subjects with WMHs regardless of whether they were from a dementia or a control group. Other studies showed that elevated diastolic BP measured years earlier, was related to the presence of WMHs. The type of BP notwithstanding, these studies suggest that the development of WMHs is a relatively slow process that is related to long-standing high BP.

Clinical Correlates

As with the risk factors associated with WMHs, the clinical correlates linked to these lesions are many and varied, due partly to the high prevalence of WMHs in healthy elderly subjects. A few of the more consistently reported clinical correlates include late-onset depression, lacunar stroke, and motor deficits, with the latter including gait disturbance, slowed motor response, poor balance, and increased risk for falling. There is also a high correlation between WMHs and dementia, with more extensive WMHs found in patients with vascular dementia (VaD), Alzheimer’s disease (AD), and dementia with Lewy bodies (DLB) than in controls. Studies have also shown that within the dementias, WMHs are more severe in cases of VaD than in either AD or DLB.

Of all the clinical associations, the relationship between WMH severity and cognitive function is perhaps the most controversial. In patients with cerebrovascular risk factors, one study found that WMHs were correlated with speed of information processing, while another found that hypertensive subjects had greater volumes of WMHs and made...
significantly more perseverative errors than normotensive controls. The latter study found that working memory and general cognitive functions were not affected. In line with these findings, de Carli et al. showed that even in healthy subjects free from vascular risk factors, severe WMHs were associated with poorer neuropsychological test scores. However, this finding is contradicted by both Kozachuk et al. and Rao et al., who reported no significant correlation between cognitive impairment and WMHs in subjects without cerebrovascular risk factors. However, the above-mentioned studies have all consisted of highly selected subjects and relatively small sample sizes. In a large, population-based study of 3,301 elderly individuals, it was found that WMHs were associated with poorer cognitive function as measured by a modified Mini Mental State Examination (MMSE) and the Digit-Symbol Substitution Test (DSST). After adjustment for age, sex, and the presence of clinically silent infarcts, the correlation co-efficients for the MMSE and DSST were -0.11 and -0.12, respectively. Although these results are statistically significant, the clinical significance of such low correlations has been questioned. However, in support of the Longstreth et al. study, the Northern Manhattan Study found that WMHs were associated with worse performance on timed cognitive tasks. In addition, it was demonstrated that there was a threshold effect, with participants having WMH volumes >0.75% of total cranial volume performing significantly slower on tasks of sensorimotor ability and cognitive flexibility.

Longitudinal studies are needed to determine the cause–effect relationship between WMHs and cognition, but unfortunately few have been conducted so far. Austrom et al. found a decline on DSST but not MMSE over an 18-month period in healthy elderly subjects with WMHs compared with those without, while no significant effect on cognitive function was found over three years in the Austrian Stroke Prevention Study despite comprehensive neuropsychological testing. By contrast, Silbert and colleagues followed 104 cognitively intact individuals for up to 13 years and found that greater total and periventricular WMH volume correlated with poorer gait performance, while increased subcortical WMH volume correlated with memory decline.

Despite the failure to resolve the matter of WMHs and their influence on cognitive function, there is evidence to suggest that WMHs may have predictive value in terms of patient outcomes. In patients with lacunar infarction, it was shown that in addition to lowered survival rate and recurrent stroke rate, the prevalence of dementia was significantly greater in patients with WMHs compared with those without. These results are supported by the prospective MRI study of Yamauchi et al., who showed that severe WMHs at baseline independently predicted the risk for stroke in a series of neurological outpatients. In addition, a longitudinal study of elderly subjects with major depressive disorder found that those with severe deep WMHs (DWMHs) had a significantly worse outcome than patients without lesions. Those with severe DWMHs were more likely to remain ill or relapse and have a significantly shorter median survival time than depressed patients without WMHs. Similarly, a study assessing the long-term prognosis in patients with symptomatic carotid artery disease found that those with extensive WMHs had a three-fold higher risk for stroke. However, the increased risk for death is not limited to those with vascular risk factors. A recent study on community-dwelling older people without a history of stroke or neurological disease showed that severe WMHs significantly increased the risk for death even after adjustment for hypertension, high cholesterol, diabetes, and coronary artery disease.

**Progression**

As there are so few longitudinal studies of WMHs, little is known about their evolution or how their progression affects clinical outcomes. Several small studies using semi-quantitative visual rating scales to assess WMHs over periods of up to five years showed that there was a mild increase in lesion load in many, but not all, subjects. Interestingly, the increase was correlated with diastolic BP at baseline, but was not associated with a change in neuropsychological test scores. Quantitative studies have shown that, in healthy subjects, the average increase in WMH volume was 1.1cm³ over four years in one study and 0.1cm³ over six years in another. However, when subjects with only punctate lesions were excluded from the analysis, those with confluent lesions showed a WMH volume increase of up to 9.3cm³ over the six years. From these results it was concluded that punctate WMHs are not progressive and are therefore clinically inconsequential, whereas early confluent and confluent WMHs are progressive and hence a cause for concern. In agreement, the recent multicenter, multinational Leukoaraiosis and Disability Study (LADIS) showed that WMH progression over three years was significantly associated with baseline WMH severity. However, the LADIS group also found that lacunes also progressed and that the appearance of new lacunes was predicted by the baseline severity of both WMHs and lacunes. The discrepancy between the results from these two studies is difficult to reconcile because it is not known whether the punctate WMHs in the study of Schmidt et al. are comparable to the lacunes in the Gouw and colleagues study. It is clear then that a consensus must be reached on a precise radiological definition of WMHs in order to avoid further confusion.

**Pathogenesis**

Despite the existence of a number of studies on the neuropathology of WMHs, the histological features of these lesions remain unresolved. It has been proposed that WMHs are part of a cerebrovascular disease continuum, with asymptomatic radiological findings and areas of incomplete subcortical infarction at one end, through to subcortical infarcts and dementia at the other extreme. While demyelination and sparing of the subcortical U-fibers are the most consistent findings, a whole range of pathologies has been reported including gliosis, axon loss, arteriosclerosis, dilated perivascular spaces, infarcts, and spongiosis (see Table 1). The lack of consensus is such that some authors even claim that pathological correlates of WMHs do not exist. This conclusion was drawn because on the one hand, direct topographic correlations could not be made between discrete MRI abnormalities and neuropathological changes, and on the other hand, areas of myelin pallor and gliosis were associated with areas of normal signal intensity. Nevertheless, a number of associations have been identified providing indirect evidence that WMHs have an ischemic origin and that blood–brain barrier (BBB) dysfunction may be involved. The unique architecture of the blood supply to the cerebral white matter is thought to underlie the ischemic nature of WMHs. The periventricular area is considered an arterial border zone because anastomoses between deep penetrating arteries are sparse, thereby rendering the periventricular area vulnerable to moderate decreases in perfusion. Similarly, the deep white matter is irrigated by long penetrating arteries that do not arborize, instead giving off short side
Extending this idea, Thomas and colleagues hypothesized that WMHs are pathological vascular changes, most probably of hypertensive origin. They found a significant correlation with the degree of histopathological arteriosclerosis. In the work of Furuta et al., who examined the sclerotic index of the medullary arteries by measuring their internal and external diameters, it was discovered that cerebral autoregulatory dysfunction was a significant and independent determinant of lesion severity. This is because an elevated CSF–serum albumin ratio indicates the presence of BBB damage. Consequently, the BBB hypothesis was obtained when BBB permeability was demonstrated by MRI following intravenous injection of a contrast agent in maturity-onset diabetes patients and controls. An intact BBB is impermeable to the contrast agent, whereas a damaged BBB allows the agent to leak into adjacent tissue thereby altering the MRI signal in these areas. Subjects with severe WMHs exhibited a greater signal intensity increase regardless of whether they had diabetes or not, indicating that those with more WMHs had increased BBB permeability compared with those with fewer lesions.

On the other hand, a contrast-enhanced MRI study of dementia patients with WMHs failed to detect any increased signal in the affected white matter regions. This was a surprising result given that half of the subjects had evidence of BBB dysfunction in the form of elevated CSF–serum albumin ratios. Therefore, Wahlund concluded that WMHs are not a consequence of BBB damage. However, it has been pointed out that this study comprised a very small sample size and the imaging technique used was much less detailed than that used by Starr et al. Nevertheless, it
should be borne in mind that raised CSF albumin levels cannot solely be attributed to disruption of the BBB because the main source of protein in the CSF is the choroid plexus, and therefore it is possible that the impairment lies with the choroid plexus and not the BBB at all.45

However, histological support for the BBB theory comes from our own work and that of others. In a study that simultaneously examined measures of gliosis, myelination, and vascular integrity (CD31), it was found that only reduced vascular integrity predicted WMH severity in a multivariate analysis.46 Furthermore, a significant reduction in the immunohistochemical expression of P-glycoprotein, a molecular efflux pump, was found in lesioned white matter compared with non-lesioned white matter, indicating BBB compromise in areas with WMHs.47 P-glycoprotein is an important constituent of the BBB because it actively transports penetrating substances from the brain parenchyma back to the blood, thus maintaining the internal environment of the brain.17,48 This work is supported by Akiguchi et al.,49 who found significantly greater levels of immunoglobulin G (IgG) extravasation in brains with WMHs than in controls without WMHs. It must be noted that these findings, which suggest that BBB dysfunction is a mechanism for the development of WMHs, do not preclude the possibility of ischemic involvement. Indeed, it has been hypothesised that as IgG extravasation was found in areas of white matter that are especially vulnerable to cerebral hyperperfusion, BBB disruption may not be the primary cause of WMHs; instead, BBB impairment may be a consequence of chronic cerebral ischemia.50

Although the histological correlates of WMHs are far from clear, there is evidence that different types of WMH may have distinct pathological features. When lesions were separated into rims, caps, bands, punctate lesions, and patches, it was shown that the rims were always associated with myelin pallor, arteriosclerosis, and gliosis. Features. When lesions were separated into rims, caps, bands, punctate lesions, and patches, it was shown that the rims were always associated with myelin pallor, arteriosclerosis, and gliosis. Punctate lesions consisted of dilated perivascular spaces and perivascular gliosis, while patches were also associated with myelin pallor and dilated perivascular spaces.31,51 This regional variation in pathology may underlie much of the variability between studies reported to date.

**Conclusion**

This article highlights many of the findings from studies of the pathogenesis of WMHs. From the literature, it is evident that these lesions are most likely the result of more than one pathological process. However, neuropathological studies have largely been descriptive and many have restricted their focus to highly selected disease groups. The pathogenesis of WMHs remains unknown, although the current view is that these lesions are predominantly ischemic in nature. With increasing evidence pointing to a BBB dysfunction, the role that BBB impairment plays in the evolution of these lesions requires further investigation. A comprehensive prospective pathological study with an emphasis on the vasculature within WMHs is needed to shed light on the full spectrum of pathological correlates underlying these lesions.

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