REVIEW

Ischemic white matter damage and cognitive impairment

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Abstract

White matter damage may play an important role in the pathogenesis of vascular dementia. White matter abnormalities are easily visualized as white matter high-intensity lesions (WML) on T2-weighted magnetic resonance images. The extent of WML may be an indicator of cognitive impairment, in particular, impairment related to frontal lobe dysfunction. However, it is unclear whether the extent of WML is an independent predictor of cognitive impairment. In patients with extensive WML, atrophy of the corpus callosum may be an important predictor of global cognitive impairment. We investigated the relationship between the extent of WML and callosal size with cognitive function in patients who had been diagnosed with lacunar stroke or no specific neurological disease. Multivariate analysis showed that only callosal size and age were significant independent predictors of mini-mental state examination scores (a measure of global cognitive function), whereas only the extent of WML was an independent predictor of the score on the verbal fluency task (a measure of frontal lobe function). Callosal atrophy may be an important predictor of global cognitive impairment in patients with WML, whereas the extent of WML per se may be related to impairment of frontal lobe function independent of callosal atrophy. White matter high-intensity lesions with callosal atrophy may indicate a severe form of white matter damage with axonal loss, the degree of which may determine the severity of global cognitive impairment. Our longitudinal study revealed an association between progression of WML and vascular risk factor status during follow up in patients with initially mild WML. Early detection of WML without callosal atrophy at a stage of subtle cognitive impairment and slowing the progression of WML to a severe form with callosal atrophy might prevent the development of dementia.

Key words: *cognition, corpus callosum, magnetic resonance imaging, white matter.*

INTRODUCTION

White matter high-intensity lesions (WML) on T2-weighted magnetic resonance (MR) images (leukoaraiosis) are frequently detected in elderly people.[1,2] In patients without a history of stroke, the extent of WML may be related to the degree of cognitive impairment.[2] Among patients with dementia of presumed vascular origin, the extent of WML may also be correlated with the severity of dementia.[1] However, it remains controversial whether the extent of WML per se is an independent predictor of cognitive dysfunction and, if so, what type of cognitive function is influenced by the extent of WML.[3,4]

ATROPHY OF THE CORPUS CALLOSUM AS AN INDICATOR OF GLOBAL COGNITIVE IMPAIRMENT

White matter damage may play a role in the pathogenesis of dementia. However, the relationship between the extent of WML and global cognitive func-

tion is not straightforward. Not all patients with extensive WML have dementia. This reveals a contribution of additional factors, which determine global cognitive function, in patients with extensive WML. If the extent of the WML on T2-weighted MRI is of the same degree, a difference in pathologies in the WML may determine the severity of white matter damage. When located in the deep and subcortical white matter, WML may reflect ischemic damage and may correspond to not only focal rarefaction of myelin, but also to loss of fibers and even lacunar infarctions according to the histopathological characteristics.[5] The severity of axonal disruption in the WML may be important as a determinant for the degree of cognitive impairment. The extent of WML, however, cannot differentiate white matter damage with axonal loss from that without axonal loss.

The corpus callosum is composed of interhemispheric fibers traversing the subcortical white matter.[6] In patients with WML, callosal atrophy may result from axonal disruption due to white matter damage. Thus, the WML with callosal atrophy may indicate a more severe form of white matter damage with axonal loss, whereas the WML without callosal atrophy may correspond to pathologies without axonal loss, including demyelination. Callosal atrophy may parallel the total loss of fibers in the white matter because the severity of ischemic damage of a nerve fiber in the white matter may not be affected by the direction of the fiber.[7] Thus, if global cognitive impairment is related to severe damage of the white matter in subjects with WML, callosal atrophy may be an important indicator of global cognitive decline. Ischemic damage of large-scale networks between cortical regions or between cortical–subcortical regions, leading to disconnection, may cause cognitive impairment associated with widespread functional disturbance.[8]

Relationship between callosal size, cognitive function and brain metabolism in patients with lacunar infarction and extensive leukoaraiosis

The purpose of the first study was to determine whether callosal atrophy is a predictor of cognitive decline in patients with extensive WML of the same degree.[9] We studied 11 right-handed male patients with lacunar infarction and diffuse WML in the bilateral hemispheric white matter on T2-weighted MR images (eight with dementia and three without dementia, according to DSM III-R criteria), aged 59–77 (mean ± SD: 67 ± 6) years. Mid-sagittal corpus callosum areas on T1-weighted images were compared with an intelligence quotient determined using the Wechsler Adult Intelligence Scale. The relationship between these parameters and the cerebral oxygen metabolism, which was measured using positron emission tomography, was also evaluated in the eight patients with dementia. Compared with 19 age and sex-matched right-handed healthy control subjects, the patients had a significantly smaller total callosal area ($4.29 \pm 0.84\ cm^2$ versus $5.92 \pm 0.79\ cm^2$). The severity of callosal atrophy, which varied from mild to severe, was significantly related to the total intelligence quotient ($r = 0.75$, $P < 0.01$; Figure 1). In the eight patients with dementia, total callosal area was significantly correlated with the mean level of oxygen metabolism in the cerebral white matter ($r = 0.87$, $P < 0.01$, the partial correlation coefficient obtained using the value of the cerebral cortex as the variable to be controlled). These findings suggest that callosal atrophy is a predictor of global cognitive decline in patients with extensive WML of the same degree. Callosal atrophy may reflect the severity and extent of white matter damage associated with a decrease in oxygen metabolism, which may determine the severity of intellectual decline in patients with WML.

EXTENT OF WML AS AN INDICATOR OF FRONTAL LOBE DYSFUNCTION

Although the extent of WML may not be an independent predictor of global cognitive dysfunction, it may be correlated with specific cognitive deficits, particularly those related to the impairment of frontal lobe functions. The severity of axonal disruption in the WML may determine the type of cognitive deficit caused by the WML. Demyelination may reduce the speed of neuronal connectivity, whereas axonal disruption may result in a loss of connectivity. Thus, mild WML without axonal damage may influence specific cognitive functions, such as those involving the speed of mental processing and attention abilities (subcortico-frontal lobe functions), without affecting performance on neuropsychological tests that mainly focus on cortical functions such as language and visuospatial abilities.[10,11] The extent of WML may be correlated with the severity of frontal lobe dysfunction, independently of the degree of callosal atrophy.

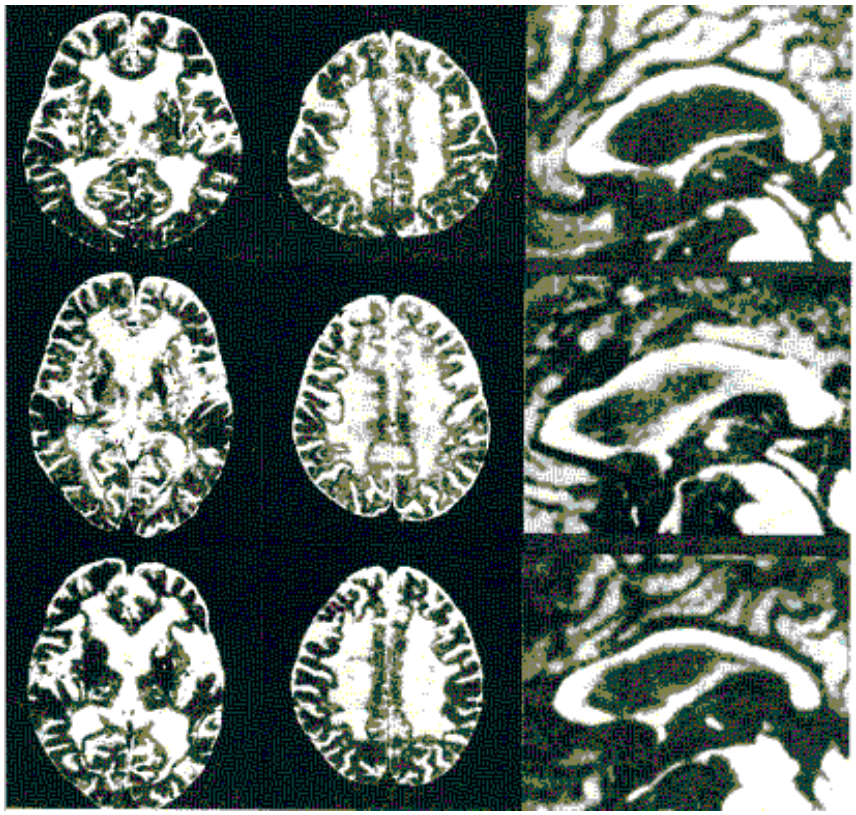

Figure 1 Examples of high-intensity lesions on T2-weighted magnetic resonance (MR) images (TR 3000 ms/TE 80 ms) (left and middle columns) and corpus callosum atrophy on T1-weighted images (TR 400 ms/TE 20 ms) (right column).[9] Upper row shows mild atrophy of the corpus callosum (no dementia, total intelligence quotient (IQ) = 107; middle row shows moderate atrophy (mild dementia, total IQ = 81); lower row shows severe atrophy (moderate dementia, total IQ < 60).

Relationship between the extent of WML, callosal size and cognitive function in patients with varying degrees of WML

The purposes of the second study were to determine whether callosal atrophy is a predictor of global cognitive decline and whether the extent of WML is a predictor of frontal lobe dysfunction independent of callosal atrophy in patients with varying degrees of severity of WML.[12] We studied 62 patients, aged 49–86 (mean ± SD: 68 ± 8) years, who underwent MRI because of neurological symptoms and were diagnosed as having lacunar stroke or no specific neurological disease: 28 with lacunar infarcts and 34 without. We adopted two cognitive measures: the mini-mental state examination (MMSE) and the verbal fluency (VF) task. The MMSE is a non-timed task that is accepted as a measure of global cognitive function, whereas the VF task is a timed task that is relatively sensitive to frontal lobe dysfunction. Mid-sagittal corpus callosum areas/skull area ratio in the anterior-half or posterior-half region on T1-weighted MR images was measured,[13] and WML in the anterior or posterior region on T2-weighted MR images were scored from 0 (none) to 8 (maximal).[14] Multivariate analyses were used to test the independent predictive value of patient age, sex, educational level, other medical illness, lacunar infarct, corpus callosum area and extent of WML with respect to scores on the MMSE or VF tasks. Stepwise multiple linear regression analysis produced a model including the anterior-half callosal area/skull area ratio and age with a correlation coefficient of 0.44 for the MMSE score: MMSE score = 1.354[anterior-half callosal area/skull area ratio] – 0.079[age] + 29.4, $P < 0.002$. In this model, the anterior-half callosal area/skull area ratio accounted for 11.8% of the variance of the MMSE score, whereas age accounted for 7.5% of the variance. After controlling for the effects of all other variables, including the posterior-half callosal area/skull area ratio, the anterior-half callosal area/skull area ratio was also a significant independent predictor of the MMSE score. Stepwise regression analysis also produced a model including the anterior WML score with a correlation coefficient of 0.354 for the score of

the VF task: VF task score = −0.523[anterior WML score] + 8.385, $P < 0.005$. In this model, the anterior WML score accounted for 12.5% of the variance of the score of the VF task. After controlling for the effects of all other variables, excluding the posterior WML score, the anterior WML score was a significant independent predictor. However, the effect of the anterior WML score on the score of the VF task was not independent of the effect of the posterior WML score, because a strong correlation was found between the anterior and posterior WML scores ($r = 0.87$, $P < 0.001$). These findings suggest that callosal atrophy, particularly in the anterior-half region, is an important predictor of global cognitive impairment in patients with WML, whereas the extent of WML per se is related to the impairment of frontal lobe function independent of callosal atrophy. Global cognitive decline in the patients examined in this study may be attributable to severe damage in the frontal white matter, which may cause disconnection between the frontal cortex and other regions.[15]

RISK FACTORS FOR PROGRESSION OF WHITE MATTER DAMAGE

The findings from this study suggest that the effect of the extent of WML per se on cognitive function may be significant, but subtle, and that WML with callosal atrophy may indicate a severe form of white matter damage with axonal loss, which may be related to global cognitive impairment and dementia. Therefore, early detection of WML without callosal atrophy at the stage of subtle cognitive impairment and slowed progression of WML to a severe form with callosal atrophy might prevent the development of dementia. Arteriolosclerosis may be the most important causative factor in the development of WML, and the extent of WML may reflect the extent of brain arteriolosclerosis.[16] Thus, aggravation of vascular risk factors, especially hypertension, leading to progression of arteriolosclerosis may cause a chronic increase in WML with time. A few population-based studies on the rate of WML progression have shown asymptomatic increases in the number and/or extent of WML in relation to hypertension.[17,18] Asymptomatic progression of WML during follow up may indicate an increased risk of stroke based on arteriolosclerosis (lacunar infarctions or hemorrhages), the occurrence of which may cause a severe form of white matter damage with axonal loss.

Significance of WML as a predictor for strokes from arteriolosclerosis

The purposes of the last study were to determine whether the extent of WML is an independent predictor of risk for subsequent strokes from arteriolosclerosis, and whether serial evaluation of WML can be used to identify patients who are at risk of strokes.[19] We prospectively followed, with serial MRI scans, 89 patients who were diagnosed as having symptomatic lacunar infarct or stroke-free, neurologically healthy patients with headaches or dizziness. No patients had significant stenosis of major cerebral arteries or atrial fibrillation. Multivariate analysis using the Cox proportional hazards model was used to test the predictive values of risk factor status at entry and during follow up, lacunar infarct, and extent of WML (scored from 0 to 16) at the baseline scans concerning subsequent stroke. During follow up (51 ± 19 months), seven strokes (five lacunar infarctions and two hemorrhages) occurred: four in nine patients with severe WML (score of 9–16), and three in 40 patients with mild WML (score of 1–8) (log-rank test; $P < 0.005$). None of the 40 patients without WML experienced stroke. The extent of WML was an independent predictor of subsequent stroke (relative risk for a one-point score increase, 1.60, 95% confidence interval, 1.02–2.54; $P < 0.05$). In three strokes among 80 patients without severe WML, two strokes occurred in four patients with an increase in the WML score during follow up, and one occurred in the other 76 patients without an increase ($P < 0.0001$). Progression of WML was associated with risk factor status during follow up (the presence of moderate hypertension, uncontrolled diabetes mellitus and smoking). After scrutinizing the risk for atherothrombotic or embolic stroke, severe WML at baseline is an independent predictor of risk for subsequent strokes based on arteriolosclerosis, even after controlling for the risk factor status during follow up. This suggests that patients with severe WML have a high risk of subsequent stroke, even if vascular risk factors are strictly controlled. Progression of WML during follow up is associated with subsequent stroke in patients with initially mild WML (Figure 2). The association between progression of WML and vascular risk factor status during follow up suggests that control of vascular risk factors may prevent the development of severe WML. Serial evaluation of the extent of WML on MRI may be used to identify patients who are at risk of subsequent strokes.

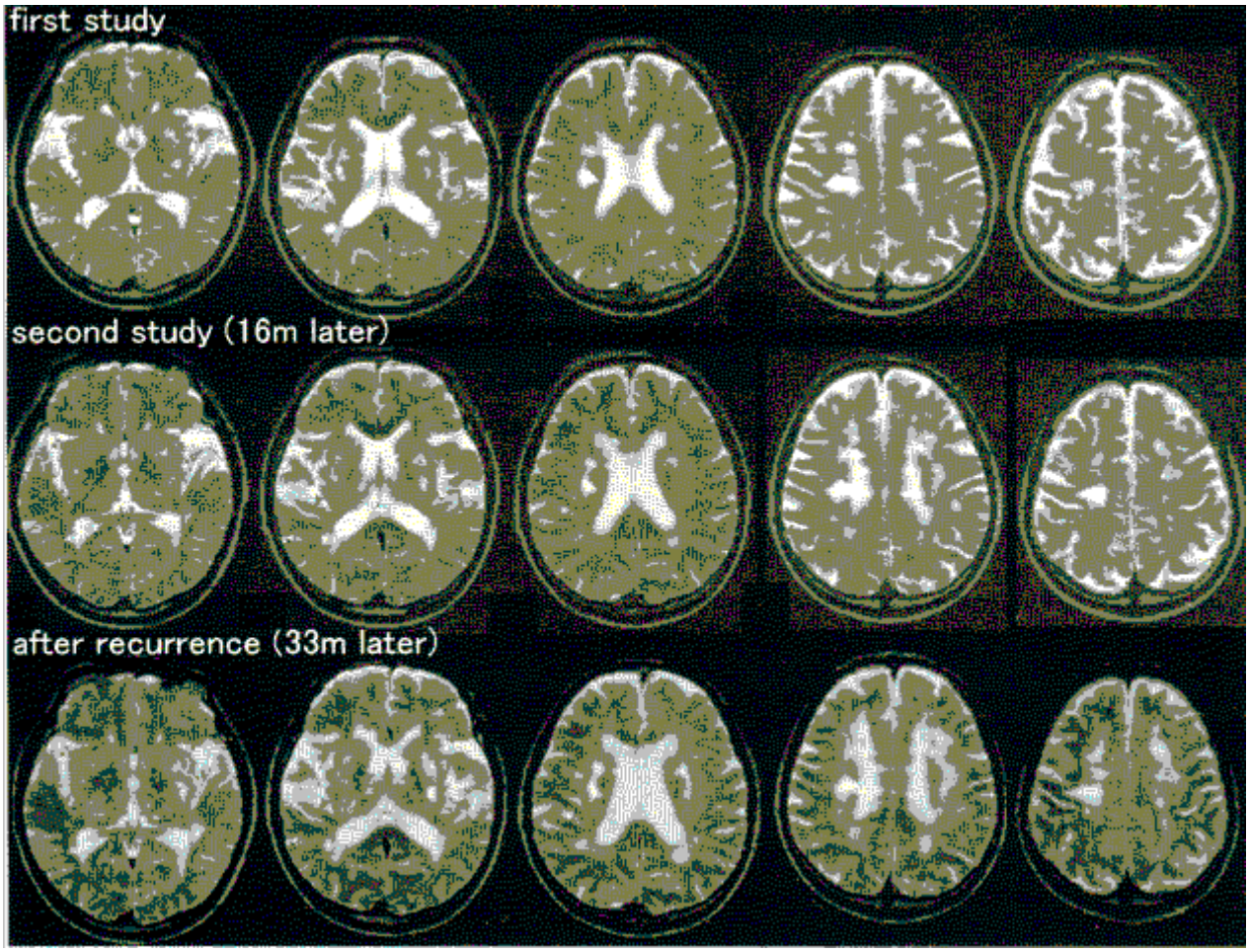

Figure 2 An example of progression of white matter high-intensity lesions (WML) before the occurrence of a stroke in a 68-year-old man with lacunar infarcts.[17] The first magnetic resonance imaging (MRI) study (top row) shows multiple lacunar infarcts in the bilateral basal ganglia and WML (score = 8). The second study 16 months later (middle row) shows an asymptomatic increase in the number and extent of WML (score = 11) in the bilateral hemispheres. At this time, the control of diabetes mellitus was poor and cholesterol level was increased. A subsequent lacunar infarction occurred 17 months after the second study, with a further increase in the extent of WML (score = 14) (bottom row).

DISCUSSION AND CONCLUSIONS

Recent population-based, longitudinal studies demonstrated that the severity of WML was the strongest predictor of the occurrence of incident infarcts that were associated with subtle cognitive deteriorations,[20] and that severity of WML was associated with the rate of cognitive decline.[21] Thus, severity of WML may be a predictor for cognitive decline as well as a predictor for stroke. We demonstrated the association between progression of WML and risk factor status during follow up. This suggests that control of vascular risk factors may prevent the development of WML, which may in turn reduce the risk of developing stroke and associated cognitive decline. However, the association between WML progression and cognitive decline remains to be demonstrated. Simultaneous evaluation of callosal atrophy may help to better define the role of WML in cognitive decline. Further studies are required to determine whether the progression of WML, with or without callosal atrophy, is associated with cognitive decline. In patients with WML, callosal atrophy may provide a putative marker for monitoring

disease progression and for future therapeutic trials to prevent the development of dementia.

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