

EDITORIAL

White Matter Changes and Cognition: Where do we Stand?

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White matter hyper intensities (WMH) of presumed vascular origin are often seen on brain magnetic resonance imaging (MRI) in older subjects and in patients with strokes and dementia. They are known to increase the risk of stroke.¹ The presence of WMH on MRI in patients having dementia raises the issue of mixed dementia, but the relative contribution from vascular factors and ongoing neurodegeneration vary from case to case and need to be weighed in individual patients before a diagnostic label is used.

Historically, the finding of altered areas of white matter attenuation on computerized axial tomography was discussed in the late 1980s by Hachinski and colleagues.² They described patchy low attenuation in the periventricular and deep white matter, which they referred to as “leukoaraiosis” literally translating as rarefaction of the white matter. In subsequent years, as MRI scans were used widely, the MRI signal changes were confirmed to be in the periventricular areas, deep white matter and are also seen to occur in the deep grey matter.³ Neuropathologically, subtle WMH on MRI were associated with microglial and endothelial activation while extensive WMH were associated with reduced density of glia and vacuolation.⁴ WMH are part of the spectrum of small vessel disease which includes lacunar (or small subcortical) ischemic and haemorrhagic strokes, micro bleeds, perivascular changes and brain atrophy.^{5,6}

Until recently, WMH were generally dismissed as inevitable consequences of “normal” advancing age. Many recent studies, however, indicate that they have important risk factor associations, emphasizing that they should not be overlooked. The effects of these on cognition are cumulative. Besides their direct effects on brain, WMH are believed to increase the risk of brain damage in the presence of other pathologies.⁷⁻⁹ The prevalence of WMH increases with increasing vascular risk

factors, like hypertension,^{10,11} diabetes,¹² smoking.^{13,14} Several studies suggest that exposure to vascular risk factors in midlife is associated with an increased risk of dementia.¹⁵⁻¹⁷ In particular, hypertension and diabetes are known to be associated with a faster decline in executive function and processing speed.¹⁸ Whether these risk factors also affect structural brain aging and cognitive performance in individuals without dementia remains unclear.

It is well recognized that vascular risk factors are common to the pathogenesis of both vascular dementia and Alzheimer’s dementia (AD).¹⁹ Apart from the occurrence of a clinical stroke, the mechanisms by which vascular factors increase the risk of AD or accelerate cognitive deterioration among patients with AD are not yet fully elucidated. WMH may not fully explain the impact of vascular factors on the brain. Other more subtle structural changes may exist and have consequences related to cognition and dementia.²⁰ The vascular brain injury could act additively or synergistically with concomitant AD pathology to produce more severe cognitive dysfunction than either process alone. This interpretation is supported by extensive clinical-pathologic data indicating that subjects with both vascular disease and AD pathology show more severe cognitive impairment during life than those with pure AD^{21,22} or require less severe AD pathology to produce the same amount of cognitive impairment.²³ The presence of vascular factor however does not question or negate the actual neurodegenerative mechanism that underlies “pure AD”.

Thus, the important question no longer is whether vascular factors contribute to dementia, but to determine their relative contribution to types of dementia in general population. This

subject is analysed by Umasundar and colleagues in this issue of the journal. Authors have investigated the prevalence of important risk factors like hypertension and diabetes in patients having AD and compared with cognitively normal age, gender matched controls. The article narrates correlation of white matter abnormalities with aging and vascular risk factors as well as cognitive abnormalities. The authors conclude that periventricular white matter hyper intensities were significantly more in the hypertensive AD group, as compared to the non-hypertensive AD group. Deep white matter hyper intensities were seen only in the control group and their severity did not show an association with gender or the presence of hypertension and diabetes. The study revealed that deep white matter abnormalities are largely prevalent in an older, cognitively normal population, and not specifically associated with AD. This is in contrast to the previous studies which appear to suggest that deep white matter changes are more representative of true ischemic insults, than those in the periventricular regions. One of the limitations of this study is the sample size and perhaps a larger dataset will be necessary to validate these observations.

In practice, this means that a clinician treating a patient with AD should acknowledge that the patient’s symptoms could be due in part or could be precipitated by vascular risk factors. In a similar fashion, in patients with vascular-related dementia, accompanying neurodegenerative pathology could partly explain the clinical presentation. We need to take into account the respective influences of both vascular risk factors and neurodegenerative pathologies. The interplay of these two often has a role in the initial manifestation or

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worsening of the patient's symptoms. The therapeutic goal is to maximize the cognitive capacity of the patient for as long as feasible. Aggressively treating vascular risk factors could potentially thwart the cognitive deterioration. However, it has not been convincingly shown in a therapeutic trial that controlling vascular factors reduces the risk of AD.

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