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Why do women have more white matter hyperintensities? Sex differences in the extent, aetiology and consequences of leukoaraiosis

Perminder Sachdev*[2], Ruth Parslow[3], Wei Wen[1,2], Kaarin Anstey[4] and Simon Easteal[5]

Address: [1]School of Psychiatry, Australia, [2]University of New South Wales, Neuropsychiatric Institute, Australia, [3]The Prince of Wales Hospital, Sydney; Orygen Research Centre, Australia, [4]Melbourne, Centre for Mental Health Research, Australia and [5]John Curtin School of Medical Research, Australian National University, Canberra, Australia

* Corresponding author

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Background

Unlike other age-related brain changes, white matter hyperintensities (WMHs) are reported to be more severe in older women than men. This study examined a large epidemiological sample of middle-aged individuals to determine sex differences in WMHs, and investigated their differential functional consequences and aetiological factors to explain the sex differences.

Materials and methods

A sample of 451 persons (men 237, women 214) aged 60–64 drawn from a large community sample underwent brain MRI scans. WMHs on T2-weighted FLAIR MRI scans were measured and topographically mapped using an automated procedure. Subjects were assessed for physical health, cognitive function, putative risk factors for cerebrovascular disease and Apolipoprotein E ε4 (Apo E4) genotyping. Regression analyses were used to examine the effect of WMHs on physical and cognitive function, and the role of risk factors for total, deep (DWMHs) and periventricular (PVWMHs) hyperintensities.

Results

The mean WMH was about 4.9 ml, representing 0.84% of the white matter. Women had more WMHs in both deep and periventricular regions, especially the latter. Hypertension and heart disease were significant determinants in men and current smoking in women. The demographic, health, blood and genetic variables explained 13.4% of variance of WMHs in men and 14.0% in women. The use of hormone replacement therapy was not associated with WMH volumesin women. Apo E4 allele did not have an association with WMHs, but interacted with physical health variables to slightly increase the risk of WMHs. WMHs were not related to cognitive function, but had an association with poor physical health and grip strength in men and women, and low manual dexterity in women.

Discussion

WMHs, especially PVWMHs, are more common in women. They have an impact on physical health even at a mild stage in both sexes. There are some differences in the significant risk factors between the sexes, but these account for <20% of the variance. Apo E4 interacts with physical health risk factors to slightly increase the risk of WMHs, but the majority of the variance is unexplained and warrants genetic and longitudinal studies to explain the genesis of WMHs. The focus should move beyond the examination for cerebrovascular disease.