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FRONTAL WHITE MATTER HYPERINTENSITY PREDICTS LOWER URINARY TRACT DYSFUNCTION IN ELDERLY WITH AMNESTIC MILD COGNITIVE IMPAIRMENT AND ALZHEIMER DISEASE

Hypothesis / aims of study

White matter hyperintensity (WMH) is detected as hyperintense signals located in periventricular and deep subcortical areas on T2-weighted images of brain magnetic resonance imaging (MRI). WMH are composed of heterogeneous pathologic changes, and are mostly related to cerebral small vessel disease (1). It has been postulated that WMH are associated with cognitive dysfunction and several geriatric conditions, such as lower urinary tract dysfunction (2-3), gait disturbance and depressive symptoms. Damage of nerve fibers connecting the cerebral cortex and subcortical regions or between cortical areas may cause various geriatric symptoms.

Lower urinary tract symptoms (LUTS) often limit activities of daily life and impair quality of life in the elderly. Several studies have reported a correlation of WMH with LUTS in the elderly (2-3). However, the role of regional WMH after adjustment for brain atrophy and confounding factors in relation to LUTS remains uncertain. The purpose of this study was to determine whether regional white matter hyperintensity (WMH) can predict LUTS in elderly with amnestic mild cognitive impairment (aMCI) or Alzheimer disease (AD).

Study design, materials and methods

Candidate patients and their caregivers provided informed consent before participation in the study. We enrolled 461 outpatients (318 female) consecutively at their initial visit. Patients were aged 65-85 years, and were diagnosed with aMCI (n=69) or AD (n=392). Patients with a history of stroke or cortical lesions on MRI, severe conditions such as cardiac failure, renal disorder, and liver dysfunction, or neurological disorders other than AD were excluded from this study.

All subjects underwent assessment with Comprehensive Geriatric Assessment batteries (CGA), Mini-Mental State Examination (MMSE) and Dementia Behavior Disturbance Scale (DBD). We examined the following LUTS: urinary difficulty, urinary frequency and urinary incontinence.

MR images were obtained using 1.5T MR scanners. WMH and brain atrophy were analyzed using an automatic segmentation program. Regional WMH was evaluated in the frontal, parietal, temporal and occipital lobes.

All analyses were performed using the Japanese version of SPSS for Windows version 19.0 (IBM Corporation, Armonk, NY, USA). WMH and brain atrophy volumes were analyzed by non-parametric tests because these variables did not show a normal distribution. To explore independent risk factors for LUTS, total and regional WMH were entered into a logistic regression model with the following variables selected as possible confounders: age, sex, MMSE, BMI, diabetes, brain atrophy and medication. Predictors of LUTS were tested by receiver operating characteristic analysis. Results were considered significant at $p < 0.05$.

Results

Mean (± SD) age of the subjects was 77.2±5.1 years, and 69% were female. The mean score of WMH was 19.2±20.1 mL, IC 1373.9±128.1 mL, PAR 1022.5±101.4 mL, CSF 351.9±60.4 mL and VCL 62.2±22.4 mL.

In age-related changes in regional WMH, at 65-69 years, the frontal and parietal lobes had greater WMH than did the temporal and occipital lobes. Frontal and parietal WMH markedly increased in size with ageing, being about twice the volumes in subjects over 80 years compared with those in subjects aged 65-69 years ($p<0.001$). WMH in the temporal lobe slowly increased in subjects over 80 years ($p=0.03$), while WMH in the occipital lobe did not significantly increase with ageing.

The frequency of urinary incontinence significantly increased with age. However, urinary difficulty and urinary frequency were not statistically different between each age group.

Older age was associated with high frequency of urinary incontinence ($p=0.033$), and patients with urinary difficulty and urinary frequency ($p<0.001$ and $p=0.007$) were predominantly male. Subjects with urinary incontinence showed a decline of cognitive function ($p<0.001$).

Significantly greater volumes of WMH in all brain regions were observed in subjects with urinary incontinence. Subjects with urinary difficulty had decreased PAR ($p=0.002$) and increased CSF and VCL volumes ($p=0.002$ and $p=0.045$). Enlargement of VCL was also observed in subjects with urinary frequency ($p=0.002$) and urinary incontinence ($p<0.001$).

The effect of regional WMH on LUTS was tested by multivariate logistic regression. Adjusting for confounding factors, the analysis indicated that male gender and use of medication for anxiety/sleeping disorder or benign prostatic hyperplasia were independently associated with urinary difficulty, while enlarged VCL and use of medication for hypertension or overactive bladder predicted urinary frequency. Regional WMH in the frontal lobe was a specific risk factor for urinary incontinence, as well as VCL, performance of MMSE, and use of medication for overactive bladder.

Interpretation of results

In this study, we reported two main findings. Firstly, WMH progressed with ageing, especially in the frontal lobe. Secondly, urinary incontinence was associated with WMH in the frontal lobe even after adjustment for brain atrophy and classical confounding factors. Our observation strongly suggests that to maintain healthy urinary function of the elderly, preventive intervention for WMH should be performed in middle age. Correction of lifestyle may delay the onset or progression of LUTS by controlling WMH. Detailed studies are needed to clarify the relevant risks, natural history and efficient treatment for WMH.

Concluding message

In conclusion, this study provides evidence of an interaction between frontal WMH and urinary incontinence in patients with AD or aMCI. WMH increased with age, especially in the frontal lobe. Urinary incontinence in the demented elderly is not an incidental event, but rather an important clinical manifestation of WMH.

References

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Disclosures

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