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Original Study

Regional White Matter Lesions Predict Falls in Patients With Amnestic Mild Cognitive Impairment and Alzheimer's Disease

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ABSTRACT

Objectives: Preventive strategy for falls in demented elderly is a clinical challenge. From early-stage of Alzheimer's disease (AD), patients show impaired balance and gait. The purpose of this study is to determine whether regional white matter lesions (WMLs) can predict balance/gait disturbance and falls in elderly with amnestic mild cognitive impairment (aMCI) or AD.
Design: Cross-sectional.
Settings: Hospital out-patient clinic.
Participants: One hundred sixty-three patients diagnosed with aMCI or AD were classified into groups having experienced falls (n = 63) or not (n = 100) in the previous year.
Measurements: Cognition, depression, behavior and psychological symptoms of dementia, medication, and balance/gait function were evaluated. Regional WMLs were visually analyzed as periventricular hyperintensity in frontal caps, bands, and occipital caps, and as deep white matter hyperintensity in frontal, parietal, temporal, and occipital lobes, basal ganglia, thalamus, and brain stem. Brain atrophy was linearly measured.
Results: The fallers had a greater volume of WMLs and their posture/gait performance tended to be worse than nonfallers. Several WMLs in particular brain regions were closely associated with balance and gait impairment. Besides polypharmacy, periventricular hyperintensity in frontal caps and occipital WMLs were strong predictors for falls, even after potential risk factors for falls were considered.
Conclusions: Regional white matter burden, independent of cognitive decline, correlates with balance/gait disturbance and predicts falls in elderly with aMCI and AD. Careful insight into regional WMLs on brain magnetic resonance may greatly help to diagnose demented elderly with a higher risk of falls.

The incidence of falls increases with age. Falls often cause fractures, disability, and injury-related death. Even if falls are not accompanied by fractures, the elderly are reluctant to be active for fear of falls.[1] In Japan, a super-aged society, falls have become not only a medical problem, but also a social and medico-economic concern.

Falls are induced by the interaction of intrinsic, pharmacologic, and environmental factors in older persons. Intrinsic risks include balance impairments and muscle weakness, which are caused by a number of sensory, neurologic, depressive, or musculoskeletal diseases. Age-related physical changes, medications, and cognitive decline also affect gait function in the elderly.[2,3] Although gait impairment is not typically seen early in the course of Alzheimer's disease (AD), patients with AD show balance impairment and a slower walking pace, and the incidence of falls in this population is approximately 3-fold higher than that of age-matched controls.[2,4] Clinical features of AD might play a role in increasing falls in the early stages of the disease. The involvement of executive dysfunction, visuoconstructional deficits, and behavior and psychological symptoms of dementia (BPSD) has been suggested.[5,6] Another factor accounting for impaired balance and gait could be the underlying burden of white matter lesions (WMLs) in AD patients.

Previous studies of the aging brain have reported the correlation of WMLs with measurements of balance, gait, and falls in the elderly.[7–14] Frontotemporal cortex and periventricular white matter are particularly vulnerable to hypoperfusion, and WMLs in these

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structures could have the consequence of impaired balance and gait in the elderly.[14] However, little is known about the interaction between WMLs and gait disturbance in dementia disorders.[7,8]

The purpose of the present study is to clarify the effects of WMLs on balance/gait function and falls in patients with amnestic mild cognitive impairment (aMCI) and AD. In the present study, we hypothesized that white matter burden (both its location and volume) is critical for manifesting clinical symptoms. We investigated the features of regional distribution of WMLs, which are responsible for deterioration of posture control and gait. Finally, we aimed to determine whether regional WMLs could be predictive to find high risk individuals for falls among elderly with aMCI and AD.

Methods

Participants

The protocol of the study was approved by the Institutional Review Board of the National Center for Geriatrics and Gerontology (NCGG), Japan. Candidate patients and their caregivers submitted informed consent before participation in the study.

We enrolled 163 patients (111 females) consecutively. Patients were >65 years old, visited the NCGG hospital in 2010 and 2011, and were diagnosed with aMCI (n = 14) or AD (n = 149). Patients were classified into a group that had experienced falls (fallers group; 63 subjects) and a group that had not experienced falls (nonfallers group; 100 subjects) in the past year. Mild to moderate AD was diagnosed as possible or probable AD according to the criteria from the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association,[15] and their total Mini-Mental State Examination (MMSE) scores were 15 or over. Patients with aMCI were diagnosed based on the criteria defined by Petersen et al.[16] Patients with severe conditions of cardiac failure, renal disorder, liver dysfunction, musculoskeletal disease, optic or neurological disorders other than AD, and patients with a history of stroke or cortical lesions on brain magnetic resonance (MR) imaging were excluded.

Evaluation of Fall Risk Factors

Experience of falls was ascertained by interviews with patients and their caregivers. Risk of falls was evaluated by the Fall Risk Index, comprising 21 questionnaires for physical function, geriatric syndrome, and environmental hazards.[17] The presence or absence of knee joint pain was examined as a subitem of the FRI. Information about previous history and medication was obtained from the patients' clinical charts. Polypharmacy was defined as taking 5 or more types of oral medicine.[18] The patient's drinking habit was assessed by 1 of the questionnaires on a 4-point scale (0: daily drinking ≥56 g ethanol, 1: daily drinking <56 g ethanol, 2: occasional drinking, 3: none). Anemia was assumed to be present if the patient's hemoglobin was less than 11.0 g/dL.

Cognitive function was evaluated by MMSE, Alzheimer's Disease Assessment Scale (ADAS), and digit span.[19,20] Depression and BPSD were estimated by the Geriatric Depression Scale-15 and Dementia Behavior Disturbance Scale, respectively.[21,22]

Balance control was assessed from the center of gravity sway during 1 minute of standing on a stabilometer (Stabilometry analysis SYSTEM GP-5000; ANIMA Co., Tokyo, Japan) with eyes opened and closed. Parameters of the postural sway included enveloped area (ENV-AREA), which is an area inside of the envelope of the center of gravity sway, total trajectory length of traced sway (LNG), and trajectory length of X direction (X-LNG) and Y direction (Y-LNG), which measure the length from displacement of sway in mediolateral and anteroposterior directions, respectively.

Gait function was evaluated by the Timed Up and Go test (TUG), tandem gait steps, and time of standing on one leg. Muscle strength was measured by a hand grip test.

Brain MR Imaging

A standard series of axial T1-weighted (repetition time [TR], 485 ms; echo time [TE], 11 ms), T2-weighted (TR, 3800 ms; TE, 93 ms) and fluid-attenuated inversion recovery (TR, 8000 ms; TE 101 ms; inversion time, 2500 ms; a 256 × 256 matrix) MR sequences of the brain were performed using 1.5 T MR scanner (Siemens Avanto, Munich, Germany). Scans in parallel with the anterior commissure-posterior commissure line were performed from the vertex to the foramen magnum with 6-mm thick slices and an interslice gap of 1.2 mm.

Rating of WMLs and Brain Atrophy

WMLs appeared as hyperintense on T2-weighted images but did not leave a clear hypointense hole on T1-weighted images. WMLs were visually assessed as periventricular hyperintensity (PVH) or deep white matter hyperintensity (DWMH). WMLs were considered periventricular if the largest diameter was adjacent to the ventricular lining; they were otherwise considered subcortical.[23] PVH was classified by a 5-point scale measured at frontal caps, wall of the lateral ventricle (bands), and occipital caps (0: no, 1: pencil thin lining <3 mm, 2: smooth halo or thick lining 3–10 mm, 3: extending caps 10–25 mm, 4: large confluent white matter >25 mm). The overall degree of PVH was calculated by adding up the scores for the 3 separate compartments.[23] The number and size of DWMH were counted in the frontal, parietal, temporal, and occipital lobes, basal ganglia, thalamus, and brain stem. The size of DWMH was classified according to the largest diameter: small (1–3 mm), medium (3–10 mm), or large (>10 mm). To calculate the volume, DWMH was assumed to be spherical with a fixed diameter of 2, 6, and 12 mm for each of the 3 respective categories.[23]

For analysis of brain atrophy, Evans ratio (ER), inverse cella media index (iCMI), caudate head index (CHI), and basal cistern index (BCI) were calculated.[23] The following were measured with slide calipers: the maximum distance between the tips of the anterior horns (A); the width between the bilateral heads of the caudate nuclei (B); the maximum transverse inner diameter of the intracranial space (C); the maximum width of the cella media (D); the maximum transverse inner diameter (E); the internal width between the bilateral temporal lobe (F); and the maximum transverse inner diameter (G). The ER, iCMI, CHI, and BCI were calculated with the following respective formulae: ER = A/C; iCMI = D/E; CHI = B/C; and BCI = F/G, respectively.

WMLs in all participants were collectively evaluated by 2 trained raters, who had no knowledge of the clinical data. To test the inter-rater reliability, the results of the 2 raters were subjected to correlation analysis for comparison in a random sample of 10 subjects. The analysis showed a strong correlation (r = 0.87–0.91, P < .0001), which suggested that the method of measurement used for this study was reliable.

Statistical Analysis

Statistical analysis was performed using SPSS 18.0 for Windows (SPSS Inc, Chicago, IL). Since WMLs did not show normal distribution, they were converted to rank variables and analyzed by nonparametric tests. Clinical information and results of neuropsychological tests, posture sway, and gait were compared between the fallers and the nonfallers by Mann–Whitney U-test. Association between WMLs and balance/gait functions was analyzed by partial Spearman rank order correlation analysis. Independent risk factors of falls were