representative Japanese elderly subjects, we organized a group of geriatric outpatient clinics, and investigated the clinical manifestations of WMLs in those patients. Especially, we analyzed the relation of WMLs with global cognitive function, depressive state, vitality/volition, and nineteen symptoms of the geriatric syndrome.

Methods

Subjects

This is a multi-center study performed at three different university geriatric outpatient clinics in Japan under the organization of a Longevity Science Research Grant from the Ministry of Health, Labour and Welfare of Japan (H15-Choju-013). Two hundred eighty six consecutive subjects (103 men and 183 women, mean±SD age; 74.5±7.8 years old) were included in this study: 187 at Kyorin University Hospital, 74 at Chiba University Hospital, and 25 at Nagoya University Hospital, from January 2004 to January 2005.

The diagnosis of dementia was made according to *the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. The definition of hypertension was systolic BP >140 mmHg or diastolic BP >90 mmHg, or

receiving anti-hypertensive drugs. The definition of diabetes was glycosylated hemoglobin A1c >6.5%, or receiving anti-diabetic drugs. The definition of hyperlipidemia was total cholesterol >5.72 mmol/L, triglyceride >1.70 mmol/L, or receiving anti-hyperlipidemic drugs.

All subjects underwent the following assessment of global cognitive and psychological function. Cognitive function was evaluated by Mini-Mental State Examination (MMSE).[16] In this examination, we focused on calculation (serial subtraction of 7 from 100) to evaluate attention and working memory (part of the frontal lobe function). We also performed verbal fluency or word recollection test by asking the subjects to name as many vegetables as possible, which is also indicative of the frontal lobe function. Depression was evaluated by 15-item Geriatric Depression Scale (GDS15), which consists of 15 dichotomous questions for screening depressive symptoms in elderly subjects (range 0-15).[17] Vitality index was used to measure vitality or volition in daily life (waking pattern, communication, feeding, getting on and off the toilet, and rehabilitation and other activities, two points each, range 0-10).[18] A full score can be maintained until one is severely disabled in cognition or function. The distribution of vitality index in the subjects of this study is shown in figure 1.

We examined symptoms of the geriatric syndrome: 19 dichotomous questions about hallucinations, delusions, insomnia, vertigo, paralysis, numbness, gait disturbance, tripping, falls, pollakiuria, urinary incontinence, constipation, decreased appetite, weight loss, apathy, speech impairment, swallowing difficulty, tremor, and muscle stiffness.

MRI image

MRI scans were performed for the diagnosis of WMLs and cerebral infarction on 1.5-T scanners (Toshiba, Japan). T1-weighted images (repetition time [TR] = 496 msec, echo time [TE] = 12 msec), T2-weighted images ([TR] = 4280 msec, [TE] = 105 msec), and FLAIR-weighted images ([TR] = 8000 msec, [TE] = 105 msec, 5 mm slice thickness) were obtained in the axial plane. MRI images were examined to differentiate between WMLs, characterized by isointense signals on T1-weighted images and hyperintense signals on T2-weighted and FLAIR images, and cerebral infarction, characterized by hypointense signals on T1-weighted images and hyperintense signals on T2-weighted and FLAIR images.

WMLs were classified as periventricular hyperintensities (PVHs), which

adjoined the lateral ventricle, and deep white matter hyperintensities (DWMHs), located in the deep white matter apart from the lateral ventricles.

PVH and DWMH Score

PVHs were evaluated in six regions in three slices: adjacent to the frontal horns, lateral ventricular body, occipital horns, frontal central semiovale in the parietal region, and occipital centrum semiovale in the parietal region in both hemispheres (Figure 2). Each area was rated as five grades according to the systematic quantification method developed by Junque et al.[11]: 0, no hyperintensities: 1, <25% of the brain area: 2, 25-50%: 3, 50-75%: 4, >75%. The sum of all grades in the six regions was defined as the PVH score (range 0-24).

DWMHs were evaluated in the frontal, temporal, parietal, and occipital lobes, and in the basal ganglia in both hemispheres (Figure 3). Each lesion was rated as three grades according to the diameter: 1, 1-3 mm; 2, 3-10 mm; 3, >10 mm, according to the study of de Groot et al.[4] The sum of all grades in five regions in both hemispheres was defined as the DWMH score. Analysis was performed assuming that the white matter scores of PVHs and DWMHs were quantitative interval scales.

Statistical Analysis

The relationship between two continuous variables such as MMSE, GDS15, or vitality index, and WML (PVH or DWMH) score was analyzed by univariate linear regression analysis, and the correlation was analyzed by means of Pearson's simple correlation coefficients. Statistical significance was set at $p<0.05$.

The relation of cognitive impairment or low vitality with PVH score or DWMH score was assessed by means of multivariate logistic regression analysis with adjustment for age, sex, hypertension, diabetes, hyperlipidemia, and past history of cerebrovascular disease, of which all variables other than age were treated as categorical data. Cognitive impairment and low vitality were defined as MMSE ≤23[19] and vitality index ≤9, respectively. Odds ratios and 95% CIs were calculated from the beta coefficients and their standard errors.

PVH score or DWMH score was compared between subjects who did or did not exhibit each symptom of the geriatric syndrome and analyzed by Student's *t* test. When the difference was considered to be significant ($p<0.05$), the difference was further assessed by means of multivariate logistic regression analysis with adjustment for age, sex, hypertension, diabetes, hyperlipidemia,

and past history of cerebrovascular disease.

Ethical Consideration

This study was approved by the ethical committees of the institutes involved in this project. We explained this study clearly, and obtained written consent from all participants and their guardians (mainly family members). All the data were stored and analyzed carefully to preserve the subjects' anonymity and protect their privacy.

Results

Clinical Data

The clinical characteristics of the study subjects are shown in Table 1. The mean age of subjects was 74.5±7.8 (mean±SD) years old, and subjects aged 65 or older comprised 88.1%. The mean body mass index was 21.8±3.3 kg/m^2 and none of the subjects was obese. Ten-point-one percent had experienced stroke or other cerebrovascular disease and 22.7% were smokers. Hypertension, diabetes and hyperlipidemia were present in 50.7%, 27.3% and 50.0% of the subjects, respectively.

WMLs

PVHs and DWMHs were observed in 77.7% and 96.7% of the total subjects, respectively. The mean score of PVHs and DWMHs was 5.5±4.8 and 35.5±39.8, respectively (Table 1). Pearson's correlation analysis showed a strong positive correlation between PVH score and DWHM score ($r=0.56$, $p<0.0001$). In relation to aging, a positive correlation was found between PVH score and age ($r=0.34$, $p<0.0001$), and between DWMH score and age ($r=0.28$, $p<0.0001$).

Cognitive and Psychological Assessment

The mean score of MMSE, GDS15 and vitality index was 23.1±5.3, 5.0±3.5 and 9.4±1.2 points, respectively, indicating that the subjects showed cognitive decline, depression, and decreased vitality, all to a mild extent. Given that a score of 23 or below on MMSE is regarded as the presence of cognitive impairment,[19] 47.5% of the subjects fell into this category. The causes of cognitive impairment were Alzheimer disease (AD) (53.3%), vascular dementia (VaD) (16.4%), combined dementia of AD and VaD (9.0%), and other types of dementia (21.3%). Pearson's correlation analysis revealed a negative

correlation between PVH score and MMSE, PVH score and vitality index, DWMH score and MMSE, and DWMH score and vitality index, respectively (Table 2). It was also found that calculation (serial subtraction of 7 from 100) was negatively correlated with PVH score ($r=-0.156$, $p=0.04$, data not shown), and verbal fluency (naming as many vegetables as possible) was negatively correlated with PVH score ($r=-0.216$, $p<0.01$, data not shown). On the other hand, no significant correlation was found between PVH score and GDS, or between DWMH score and GDS. Multiple logistic analysis revealed that PVH score and DWMH score remained significant determinants of cognitive impairment (MMSE ≤23) and low vitality (vitality index ≤9) after adjustment for age, sex, presence of hypertension, diabetes, hyperlipidemia, and past history of cerebrovascular disease (Table 3).

One hundred and ninety subjects reported symptoms of the geriatric syndrome. The frequency is shown in Table 4. Frequent symptoms (>20%) were tripping (32.1%), constipation (26.3%), gait disturbance (23.2%), and pollakiuria (22.1%). Student's *t* test showed that PVH score was significantly greater in subjects who exhibited the following symptoms of the geriatric syndrome: hallucinations, delusions, gait disturbance, tripping, falls, pollakiuria, urinary

incontinence, weight loss, apathy, swallowing difficulty, tremor, and muscle stiffness. Multiple logistic analysis revealed that PVH score remained a significant determinant of hallucinations, tripping, pollakiuria, urinary incontinence, weight loss, apathy, and swallowing difficulty after adjustment for age, sex, presence of hypertension, diabetes, hyperlipidemia, and past history of cerebrovascular disease (Table 5). By the same method, DWMH score was significantly greater in subjects who exhibited the following symptoms of the geriatric syndrome: hallucinations, delusions, gait disturbance, tripping, falls, pollakiuria, urinary incontinence, and constipation. Multiple logistic analysis revealed that DWMH score remained a significant determinant of hallucinations, delusions, tripping, urinary incontinence, and constipation after adjustment for age, sex, presence of hypertension, diabetes, hyperlipidemia, and past history of cerebrovascular disease (Table 6).

Discussion

Elderly persons are affected by multiple chronic diseases. Once they are affected by serious illness, full recovery cannot be expected with medical treatment, because elderly patients are often trapped in a vicious circle of illness

and poor quality of life (QOL). This is the reason why care and welfare contribute to the total wellbeing of the elderly. Physicians need to pay great attention to improving QOL as well as treating illness. Thus, it is important to comprehend the whole picture of their life by means of comprehensive geriatric assessment, which evaluates multiple aspects of an elderly person's life such as activity of daily life, cognition, mood, vitality, communication, and social environment.

The present study confirmed a negative correlation between the severity of WMLs and MMSE score. Multivariate analysis showed that the presence of WMLs was a significant risk factor for cognitive impairment, even after adjustment for confounding factors of age, sex, hypertension, diabetes, hyperlipidemia, and past history of cerebrovascular disease. The mechanism and the size and location of WMLs that impair cognitive function are not yet clear. However, from previous studies, it seems convincing that a reduction of blood flow in the frontal lobe plays an important role in cognitive impairment in elderly people who exhibit WMLs.[21,22] Clinical manifestations of WMLs include attention deficit and a decline in information-processing ability.[4,13,23] Junque et al. reported the reappearance of primitive reflexes, one of the symptoms of frontal lobe dysfunction, in patients with WMLs.[11] In this study, patients with PVH showed

attention deficit (incapability of calculation) and verbal inarticulacy (naming less number of vegetables), implying the impairment of frontal lobe function. WMLs, as reported previously,[6,24] were negatively correlated with vitality. Multiple logistic regression analysis, using potential risk factors including advanced age as confounding variables, found that the presence of WMLs was an independent risk factor for low vitality. Additionally, a relation between PVH score and apathy, a significant symptom of the geriatric syndrome, was also found. From previous studies showing the importance of frontal lobe function in vitality,[25-27] we assume that blood flow reduction in the frontal lobe may account for the apathy and low vitality in patients with WMLs. More precisely, WMLs disrupting the frontal-subcortical circuit may result in dysfunction in the anterior cingulate and dorsolateral prefrontal circuits, thereby leading to apathy and decreased vitality.[5,6,21] Increase in PVH score or DWMH score was not apparently correlated with depression, probably because depression is associated with many factors such as aging, female sex, hyperlipidemia, and medication.[28-30] The subjects in this study were mostly elderly (88.1%) and female (74.0%). We assume that these confounding conditions made it difficult to prove a true relation between WMLs and depression. From analysis of the association of

WMLs with the geriatric syndrome, it appears that WMLs have a relation to psychiatric symptoms (hallucinations and delusions), gait abnormalities (gait disturbance, tripping, and falls), urinary symptoms (pollakiuria and urinary incontinence), and possibly with parkinsonism (swallowing difficulty, tremor, and muscle stiffness). It was reported that WMLs were related to gait abnormalities,[5-7] presumably caused by disruption of the frontal-subcortical circuit.[31] Some other studies suggested that parkinsonism is also a contributing factor to gait disturbance in patients with WMLs.[6,32] Interestingly, we found that both gait abnormalities and symptoms of parkinsonism were associated with WMLs.

The present study confirmed an association between WMLs and voiding dysfunction (pollakiuria and incontinence). It was reported that urinary dysfunction was derived from damage to the frontal-subcortical circuit.[5,21] In relation to the symptoms of parkinsonism (swallowing difficulty, tremor, and muscle stiffness), this association was previously explained by dysfunction of the frontal-subcortical circuit.[6,32] The importance of this lesion was also suggested by a study showing that swallowing difficulty occurs with dysfunction of internuncial neurons that link the brain stem to the cerebral cortex.[33]

Considering the cause of manifestation of the geriatric syndrome in patients with WMLs, it appears that damage to associative pathways in the frontal and subcortical regions due to ischemic hypoperfusion is an important mechanism.[5,21,22] It is necessary to localize the responsible connecting pathway for each symptom by a sophisticated approach in the future.

In conclusion, we showed that WMLs were associated with cognitive impairment, low vitality, and the geriatric syndrome of psychological disorders, gait disturbance, urinary problems, and parkinsonism. Evaluating WMLs in relation to the geriatric syndrome and building a preventive measure against WMLs is an important future task for maintaining the independence of elderly people.

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