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The cross-sectional and longitudinal relationships between white matter hyperintensities and dementia in patients with Parkinson's disease: A retrospective analysis of 132 patients in a single center

Seung-Jae Lee*, Dong-Geun Lee

Department of Neurology, Sejong General Hospital, Bucheon, South Korea

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ABSTRACT

Objective: To clarify the cross-sectional and longitudinal relationships between white matter hyperintensities (WMH) and dementia in Parkinson's disease (PD) patients.
Methods: One hundred thirty-two PD patients were included. Using medical records, the patient data including Hoehn and Yahr stage, postural instability, neuropsychological tests and magnetic resonance imaging were analyzed. The degree of WMH was rated according to a modified Fazekas scale. The relationship between the variables and dementia was analyzed using the independent *t*-test, the chi-square test, logistic regression analysis and the Cox proportional hazard model.
Results: The mean age of the study patients (35 males and 97 females) was 71.6 years (range, 45–93 years). The baseline WMH was associated not only cross-sectionally with the contemporary prevalence of dementia but also longitudinally with subsequent occurrence of dementia in the univariate analysis. These relationships became attenuated and statistically insignificant in the multivariate analysis after adjusting for confounders. It was postural instability that consistently predicted dementia in both the cross-sectional and the longitudinal data.
Conclusions: Our study showed that baseline WMH was not independently associated with dementia, and instead postural instability revealed at first examination can be a more reliable predictor of dementia in PD patients.

1. Introduction

White matter hyperintensities (WMH), seen on fluid-attenuated inversion recovery (FLAIR) magnetic resonance images (MRI), generally signify the burden of small-vessel pathology in the subcortical area of the brain; they increase with age and cerebrovascular risk factors (Norrving, 2015). WMH have been known to be associated with increased risk of cognitive decline and dementia in elderly persons (Debette & Markus, 2010).

In addition, recent data have shown a significant association between WMH and cognitive impairment in patients with Parkinson's disease (PD) (Lee et al., 2010; Shin et al., 2012; Kandiah et al., 2013, 2014; Sunwoo et al., 2014). However, most studies were based on only cross-sectional data (Lee et al., 2010; Shin et al., 2012; Kandiah et al., 2013), and there are few longitudinal studies that examine the effect over time of the baseline WMH burden on cognition in PD (Kandiah et al., 2014; Sunwoo et al., 2014). Therefore, in this study, we attempt to clarify the relationship between WMH and dementia in PD patients using cross-sectional and longitudinal data from our 12 years of experience.

2. Methods

2.1. Patients and clinical assessments

Using the PD registry of our hospital, the present authors ascertained the names and registry numbers of 302 patients who came to the hospital's neurology department for initial diagnosis between January 2001 and January 2013; PD was diagnosed according to the clinical diagnostic criteria of the Parkinson's UK Brain Bank (Hughes, Daniel, Kilford, & Lees, 1992), and patients with clinical signs of vascular parkinsonism were excluded (Rektor, Rektorová, & Kubová, 2006; Kalra, Grosset, & Benamer, 2010). We then retrospectively reviewed their medical records. Thus, from the 302 patients, 170 patients were additionally excluded from this

* Corresponding author at: Department of Neurology, Sejong General Hospital, 91-121, Sosabon2-dong Sosa-gu Bucheon-si, Gyeonggi-do 422-711, South Korea.
E-mail addresses: neurosj@catholic.ac.kr (S.-J. Lee), lee0324@gmail.com (D.-G. Lee).

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study: 32 patients with an atypical course that was distinct from that of "idiopathic PD" (early severe dysautonomia, supranuclear gaze palsy, cerebellar signs, negative response to large doses of L-dopa, etc.); 29 patients with advanced dementia (initial score of Mini-Mental State Examination [MMSE] ≤ 10); 4 patients with a significant sequelae of stroke (modified Rankin scale ≥ 2); 40 patients who showed subsequent symptom recovery with no need for anti-Parkinson drugs (these patients had been diagnosed as having probable drug-induced parkinsonism); 48 patients with less than 18 months of follow-up; 16 patients with no brain MRI; and 1 patient with severe degenerative joint disease that affected the patient's gait. Finally, 132 patients with PD were included in this analysis.

At the included patients' first visits, baseline clinical information including age, gender, duration of Parkinsonian symptoms, education level, Hoehn and Yahr stage (H & Y) and vascular risk factors was investigated by the attending physician. In the L-dopa-naïve state, the presence or absence of rest tremor, rigidity and postural instability was recorded. Postural instability was defined as the presence of retropulsion or fall in the response to the pull test.

2.2. MR imaging and WMH grading

All patients underwent 1.5-T MRI and neuropsychologic tests within a month of the first visit. The MRI consisted of FLAIR imaging, three-dimensional time-of-flight intracranial MR angiography (MRA) and contrast-enhanced MRA including extracranial carotid and vertebral arteries. Stenoses of brain vessels on MRA were classified as intracranial or extracranial based on the location of the arterial stenosis. More than 50% signal loss on MRA was considered to be significant to the categorization of the stenosis pattern.

Using the modified Fazekas scale (Pantoni et al., 2005), the degree of WMH based on the FLAIR sequence was rated by the two neurologists (S.-J.L. and D.-G.L.), who were blinded to the clinical data. The modified Fazekas scale ranges from grade 1 to grade 3. The grades reflect the following: grade 1 (mild) = punctate lesions with single lesions < 10 mm and areas of "grouped" lesions < 20 mm in any diameter; grade 2 (moderate) = early confluent lesions with single lesions of 10–20 mm, areas of "grouped" lesions ≥ 20 mm in any diameter, and no more than "connecting bridges" between individual lesions; grade 3 (severe) = single lesions or confluent areas of hyperintensity ≥ 20 mm in any diameter. The WMH severity was dichotomized into two categories: Fazekas grade ≥ 2 and grade < 2. This visual rating showed good inter-rater agreement (kappa value 0.89; $P < 0.001$). The final grade was determined by the consensus of 2 investigators.

2.3. Dementia diagnosis and follow-up

The neuropsychologic tests included the Korean version of the MMSE, the Global Deterioration Score (GDS) and the Korea Instrumental Activities of Daily Living (K-IADL). The diagnosis of dementia was based on the criteria for dementia in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (American Psychiatric Association, 1994). Particularly, through interviews with each patient's caregiver, instrumental functional capacity was repetitively measured using the K-IADL, which had been validated with a sensitivity of 83% and a specificity of 82% in the diagnosis of dementia; the score cut-off point of 0.43 was used as the criterion for significant functional limitation and a dementia diagnosis (Kang, Choi, Lee, Kwon, & Na, 2002).

All patients were followed up by outpatient clinic attendance every one to three months. Based on a physician's judgment, the neuropsychological tests were repeated every three to twelve months, and the occurrence of dementia was monitored.

2.4. Statistical analysis

Statistical analyses were performed with SPSS software, version 18.0 (SPSS Inc., Chicago, IL). In the cross-sectional study on the 132 patients, the differences between the patient groups with and without dementia were compared using the independent *t*-test or chi-square test. Multivariate logistic regression was performed to determine the variables that were associated with dementia. In the longitudinal study on initially nondemented, 96 patients, the differences between patients with Fazekas grade ≥ 2 and those with grade < 2 were compared using the independent *t*-test or chi-square test. In addition, univariate and multivariate Cox proportional hazards models were used to determine the association between the baseline WMH and the future occurrence of dementia. Odds ratios, hazards ratios and 95% confidence intervals were obtained. *P*-values < 0.05 were considered statistically significant.

3. Results

The mean age of the 132 study patients (35 males and 97 females) was 71.6 years (range, 45–93 years) at the first visit. Table 1 shows the baseline characteristics of the patients with and without dementia at the initial work-up. Compared with the non-demented group, the patients with dementia were older and had significantly less education, higher H & Y stages, and higher prevalence of postural instability and Fazekas grade ≥ 2. There were no significant differences in the frequency of vascular risk factors, azotemia or stenotic lesions in the brain vessels between the two groups (Table 1).

Table 1
General characteristics of the patients with and without dementia at the initial work-up; mean ± SD, *n*(%).

	Dementia at initial work-up		*P*
	Absent (*n* = 96)	Present (*n* = 36)	
Age	70.6 ± 7.1	74.0 ± 8.2	0.010
Male	27 (28.1)	8 (22.2)	0.658
Disease duration	1.9 ± 1.9	2.5 ± 2.4	0.149
Age at onset of PD symptom	68.7 ± 6.9	71.9 ± 8.2	0.028
Education, yr	5.6 ± 4.4	3.7 ± 3.8	0.023
MMSE	25.2 ± 2.9	17.4 ± 3.6	<0.001
GDS	2.5 ± 0.5	3.8 ± 0.6	<0.001
K-IADL	0.11 ± 0.11	0.75 ± 0.47	<0.001
H&Y	1.87 ± 0.66	2.33 ± 0.68	0.001
Rest tremor	84 (87.5)	27 (75.0)	0.108
Rigidity	74 (77.1)	33(91.7)	0.080
Postural instability	21 (21.9)	19 (52.8)	0.001
Fazekas grade ≥ 2	24 (25.0)	19 (52.8)	0.003
Vascular risk factors			
Hypertension	67 (69.8)	27 (75.0)	0.668
Diabetes	30 (31.3)	6 (16.7)	0.125
Hyperlipidemia	48 (50.0)	20 (55.6)	0.696
Current smoking	5 (5.2)	2 (5.6)	1.000
Previous history of stroke	5 (5.2)	2 (5.6)	1.000
Ischemic heart disease	31 (32.3)	10 (27.8)	0.677
Atrial fibrillation	9 (9.4)	3 (8.3)	1.000
Valvular heart disease	8 (8.3)	2 (5.6)	0.727
Azotemia (Cr ≥ 1.5)	10 (10.4)	3 (8.3)	1.000
Stenosis (intracranial or extracranial)	27 (28.1)	11 (30.6)	0.830

PD, Parkinson's disease; MMSE, Mini-Mental State Examination; GDS, Global Deterioration Scale; K-IADL, Korean Instrumental Activities of Daily Living; H&Y, Hoehn and Yahr scale.

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