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The Influence of White Matter Hyperintensities on the Clinical Features of Parkinson's Disease

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This study was designed to investigate the influence of white matter hyperintensities (WMH) on clinical features of Parkinson's disease (PD) patients. The study subjects were 44 patients with PD who took a brain MRI. The severity of Parkinsonian symptoms was assessed in both 'on' and 'off' states, using the UPDRS-motor score. Thirteen patients (30%) showed WMH. The patients with WMH were significantly older than those without WMH (67±5.7 vs 60±6.4 years). In both 'off' and 'on' states, the gait scores were significantly higher in patients with WMH than in those without WMH (1.6±0.18 vs 1.1±0.12, $P<0.05$), but other motor symptom (tremor, bradykinesia, rigidity) scores between the two patient groups were not statistically different. After taking a single dose of oral levodopa/benserazide (200mg/50mg), the patients with WMH showed significantly less improvement in bradykinesia score than those without WMH (25±4.1% vs 40±4.0%, $P<0.05$), but the improvements in other symptoms were comparable between the two groups. These results suggest that WMH on MRI may influence Parkinsonian motor symptoms, particularly gait symptom and levodopa-responsiveness to bradykinesia symptom.

Key Words: Parkinson's disease, magnetic resonance imaging, white matter, levodopa, aging

Recent improvement in imaging techniques of the brain has drawn attention to the occurrence of diffuse lesions of white matter, termed leukoencephalopathy (Valentine *et al.* 1980; Loizou *et al.* 1981). The clinical significance of these abnormalities was not clearly understood, but patients with a diffusely diminished density of white matter on computed tomography (CT) were often found to have some degree of cognitive impairment or focal neurological signs (Steingart *et al.* 1987; Gupta *et al.* 1988). Magnetic resonance imaging (MRI) has proved to be more sensitive than CT in detecting these white matter lesions (George *et al.* 1986; Erkinjuntti *et al.* 1987). The hypodense lesions on CT correspond well with areas of increased signal intensity in T2-weighted MR images. These lesions seen on MRI were often termed as periventricular or white matter hyperintensities (WMH) (Zimmerman *et al.* 1986; Kertesz *et al.* 1988; Piccini *et al.* 1995).

WMH is more frequently observed in elderly people than in young people (Awad *et al.* 1986; George *et al.* 1986). In addition, patients with idiopathic Parkinson's disease (PD) have more WMH than age-matched healthy people (Stern *et al.* 1989; Bowen *et al.* 1990; Mirsen *et al.* 1991; Piccini *et al.* 1995). However, the impact of WMH on clinical features of PD has yet to be clarified.

MATERIALS AND METHODS

Study subjects were 44 patients with PD (22 men and 22 women) who took a brain MRI. The diagnosis of PD was made using the criteria of the CAPIT Committee (1992). We excluded patients with any structural lesion on MRI except WMH. All patients

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had been under levodopa therapy for more than 6 months and had shown stable responses.

The severity of Parkinsonian symptoms was assessed using the Hoehn and Yahr stage and the UPDRS-motor examination scale, before ('off' state) and about 90 minutes after the oral administration of levodopa/benserazide 200/50 mg ('on' state). The patients were asked not to eat or take antiparkinson medications for at least 12 hours prior to the assessment. Among the UPDRS-motor examination scales, we defined the tremor score as the sum of 'tremor at rest' scales (#3~7); the rigidity score as the sum of 'rigidity' scales (#10~14); the bradykinesia score as the sum of 'finger taps', 'hand movements', 'rapid alternating hand movements', 'leg agility' and 'body bradykinesia and hypokinesia' scales (#15~22 and #27); and the gait score as the 'gait' scale (#25). The responsiveness of each score to levodopa was calculated as {('off' state score − 'on' state score)/'off' state score} × 100(%). The disease progression index was calculated as (Hoehn and Yahr stage or UPDRS motor examination score)/symptom duration (years) (Piccini *et al.* 1995). Depression was checked using the Beck depression inventory (Beck, 1967). Hypertension was defined as either systolic pressure > 140 mmHg or diastolic pressure > 95 mmHg.

MRI examination was performed with a Signa 1.5T (G.E., Milwaukee) and a spin-echo sequence using proton-density (TR 2500 / TE 30 msec), T1 (TR 400 / TE 12 msec) and T2 weighting (TR 2800 / TE 80 msec). Images through the whole brain were acquired in the transverse plane with a slice thickness of 7 mm. We determined the presence of WMH using proton-density and T2-weighted images, and classified it as deep hyperintensities (DH) and periventricular hyperintensities (PH) according to 'Fazekas' method (1989) (Fig. 1). Patients with WMH were defined as WMH (+), while those without WMH were assigned to WMH (−).

Data were expressed as mean ± standard deviation. Statistical analysis included unpaired t-test, X^2-test, Mann-Whitney test and stepwise regression analysis. P values less than 0.05 were regarded as significant.

RESULTS

Thirteen patients (30%) showed WMH on MRI, among whom 5 showed DH and 8 showed PH. Table 1 shows the clinical profiles of WMH (+) and WMH (−) patients. The mean age of WMH (+) was significantly higher than WMH (−), but other profiles including gender distribution, symptom duration, the depression score and the frequency

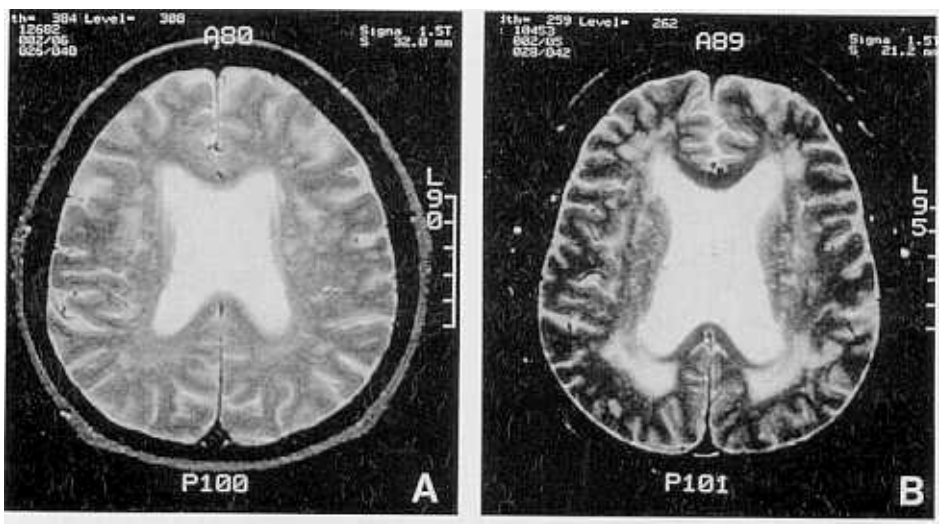

Fig. 1. T2-weighted MRI (TR 2500 / TE 80 msec) indicates (A) deep hyperintensities (DH) and (B) periventricular hyperintensities (PH).

Table 1. Clinical features

Variables	WMH(+) (n=13)	WMH(−) (n=31)	P-value
Age	67 ±5.7	60 ±6.4	.0007††
Sex - Male	5	17	.5087
Female	8	14	
Symptom Duration	3.7±1.6	3.8±1.9	.8575
Depression*	19 ±9.1	24 ±9.3	.1474
Hypertension	3(23%)	5(16%)	.9070

*: Checked by Beck Depression Inventory
Analyzed by unpaired t-test & X^2-test (for sex and hypertension)
††: significant

Table 2. Parkinsonian motor symptoms

Symptoms	WMH(+)	WMH(−)	P-value
Off:			
UPDRS-motor	34±11.6	28±11.0	.1041
Tremor	4.2± 3.8	2.9± 3.3	.2577
Bradykinesia	14± 5.2	12± 5.2	.3806
Rigidity	6.5± 3.1	5.6± 3.4	.4004
Gait	1.6± 0.7	1.1± 0.7	.0323*
On:			
UPDRS-motor	24±12.2	19± 9.2	.1012
Tremor	1.8± 3.0	1.0± 1.4	.2757
Bradykinesia	10.6± 5.5	7.8± 4.5	.0817
Rigidity	4.2± 2.9	4.1± 3.2	.8726
Gait	1.2± 0.6	0.8± 0.7	.0393*

Analyzed by unpaired t-test; *: significant

of hypertension were not significantly different between the two groups. Among 15 patients who were age 60 or less, WMH was observed in only one patient (6.7%), while it was found in 12 (41.4%) among 29 patients over age 60 ($p<0.05$).

The gait score was significantly higher in WMH (+) than in WMH (−), in both 'on' and 'off' states. WMH (+) showed a higher 'on' state bradykinesia score than WMH (−), but this difference did not attain statistical significance ($P<0.08$). The severity of other parkinsonian symptoms were not significantly different in both 'on' and 'off' states between the two patient groups (Table 2). The responsiveness of the bradykinesia score to a single dose of levodopa/benserazide in WMH (+) was

Table 3. % Improvements in Parkinsonian motor symptoms

Symptoms	WMH(+)	WMH(−)	P-value
UPDRS-motor	31±16	35±17	.4551
Tremor	71±37	70±32	.8885
Bradykinesia	25±15	40±22	.0301*
Rigidity	33±32	27±27	.5223
Gait	22±32	33±44	.4287

Analyzed by unpaired t-test; *: significant

Table 4. Disease progression index*

Variables	WMH(+)	WMH(−)	P-value
Stage	.86±.57	.73±.49	.4576
UPDRS-motor	11.5±6.6	9.2±5.4	.2337

*: Calculated as (stage or UPDRS − motor score)/symptom duration (years)
Analyzed by unpaired t-test

25%, which was significantly lower than that of WMH (−) (40%) ($p<0.05$), but the responsiveness to other symptoms in WMH (+) was not significantly different from that in WMH (−) (Table 3). In order to exclude the influence of patient age on the severity and levodopa responsiveness of parkinsonian symptoms, we performed stepwise regression analysis using the presence of WMH and patient age as independent variables, which revealed the presence of WMH was the only significant variable influencing the severity of gait symptoms and levodopa responsiveness to bradykinesia symptoms. There was no significant difference in the disease progression index between the two patient groups (Table 4).

Patients with DH showed relatively more severe parkinsonian symptoms and less levodopa responsiveness, particularly in rigidity and gait scores, than those with PH, but the number of patients appeared to be too small to attain statistical significance (Table 5).

DISCUSSION

The prevalence of WMH in healthy people is

Table 5. Clinical features between DH and PH

Variables		DH(n=5)	PH(n=8)
General	Age	65 ±3.1	69 ±6.6
	Symptom Duration	3.8±2.1	3.5±1.9
Parkinsonian Symptoms			
Off	UPDRS-motor	39 ±15.4	31 ±8.0
	Tremor	6.6±3.8	2.8±3.2
	Bradykinesia	14 ±7.4	13 ±3.8
	Rigidity	6.6±2.9	6.5±3.4
	Gait	1.8±.84	1.5±.53
On	UPDRS-motor	30 ±17.2	20 ±6.6
	Tremor	3.0±3.7	1.0±2.5
	Bradykinesia	12.2±8.0	9.6±3.3
	Rigidity	5.6±3.4	3.4±2.3
	Gait	1.6±.55	1.0±.53
% Improvements			
	UPDRS-motor	28 ±20	33 ±14
	Tremor	63 ±38	79 ±38
	Bradykinesia	23 ±21	26 ±11
	Rigidity	22 ±27	41 ±34
	Gait	7 ±15	31 ±37
Speed of Progression			
	Stage	.93±.68	.83±.49
	UPDRS-motor	13 ±8.5	11 ±5.1

Analyzed by Mann-Whitney test; none of the above comparisons is significant.

about 20 to 40% (Bradley *et al.* 1984; Mirsen *et al.* 1991; van Swieten *et al.* 1991; Piccini *et al.* 1995), although some authors reported it was over 90% in an elderly population (Awad *et al.* 1986; Zimmerman *et al.* 1986). The main reason for these variable results appears to stem from the variable criteria for WMH employed in each study. Some authors regarded small focal lesions around the frontal horn as normal, while others considered them as WMH. We also disregarded hyperintensities scattered in deep white matter if their size was too small to be pathologic lesions. Compared with age-matched healthy people, patients with PD or Parkinsonism showed significantly more WMH (Stern *et al.* 1989; Piccini *et al.* 1995). In this study, WMH was observed in 30% of patients, which is slightly less than the previously reported incidence of WMH in PD patients (Piccini *et al.* 1995), in which 37% of PD patients and 21% of age-matched controls showed WMH.

The prevalence of WMH increases with aging (Awad *et al.* 1986; Kertesz *et al.* 1988; Lechner *et al.* 1988; Fazekas, 1989; van Swieten *et al.* 1991). Our WMH (+) patients were also significantly older than WMH (−). Moreover, WMH was observed infrequently (6.7%), in patients who were age 60 or less, while 41.4% of patients over age 60 showed WMH. These results suggest that aging also significantly affects the prevalence of WMH in patients with PD in a similar fashion to that in healthy people.

After an extensive Medline search, we found that only a few studies have investigated the clinical impact of WMH on PD, which revealed that PD patients with WMH showed more severe symptoms of bradykinesia, gait disturbance and postural instability, and a more rapid course of disease progression than those without WMH (Piccini *et al.* 1995) and that patients compatible with suspected vascular Parkinsonism showed more WMH than those with PD (Zijlmans *et al.* 1995). Since Zijlmans et al's (1995) criteria for vascular Parkinsonism included predominant gait symptoms, prior studies commonly demonstrated the relationship between WMH and Parkinsonian gait symptoms. This study also showed higher gait scores in WMH (+) than in WMH (−), which is quite consistent with previous reports (Piccini *et al.* 1995; Zijlmans *et al.* 1995). In addition, we also compared the levodopa responsiveness of each Parkinsonian symptom, which revealed significantly less levodopa responsiveness to bradykinesia symptom in WMH (+) than WMH (−). Piccini *et al.* also documented more severe bradykinesia symptom in PD patients with WMH, which is compatible with our results (Piccini *et al.* 1995).

Durso *et al.* documented that the magnitude of antiparkinsonian response to levodopa, particularly bradykinesia and gait symptoms, in Parkinsonian patients was influenced by age (Durso *et al.* 1993). Since the WMH (+) group was significantly older than WMH (−), the more severe gait symptoms and less levodopa responsiveness to bradykinesia observed in WMH (+) than WMH (−) could be simply related to aging rather than the presence of WMH. Thus, to exclude the possible influence of patient age on our results, we performed stepwise regression analysis using the presence of WMH and patient age as independent variables. This analysis

revealed the presence of WMH was the only significant variable influencing the severity of gait symptoms as well as the levodopa responsiveness to bradykinesia in our patients.

Fazekas classified WMH into PH and DH, and suggested these lesions had different pathogenetic mechanisms; DH was related with cerebrovascular risk factors, while PH had no relationship (Fazekas, 1989). Leys *et al.* suggested that PH reflected a reduction in myelin density related with secondary Wallerian degeneration from white matter lesions (Leys *et al.* 1991). Piccini *et al.* demonstrated that parkinsonian patients with PH showed more severe symptoms and rapid progression, while those with DH did not show any clinical differences compared to those without WMH (Piccini *et al.* 1995). We also divided WMH (+) into PH and DH, but failed to demonstrate any significant differences between them, probably due to the limited number of patients in each group.

The mechanism as to how WMH affects symptoms of bradykinesia and gait disturbances is unclear. Although Piccini *et al.* defined PD with PH as a different clinical subtype of PD, the strong relationship between WMH and aging in PD raises the possibility that WMH is more closely associated with age-related changes than disease-specific lesions (Piccini *et al.* 1995). Since PD patients show more age-related changes of the brain, such as atrophy, than age-matched healthy people, the more WMH found in brains of PD patients may simply reflect these phenomena. Considering the fact that both bradykinesia and gait symptoms of PD are primarily linked to frontal lobe function (Watts and Mandir, 1992; Delwaide and Gonce, 1993), WMH may represent lesions in pathways connecting the basal ganglia and frontal lobe, whether they are cerebrovascular lesions (DH) or secondary myelin reduction (PH). The observation that, in PD, PH is mainly located in the anterior portion of periventricular white matter (Piccini *et al.* 1995) lends additional support to this hypothesis. Further studies using either detailed neuropsychological tests assessing the frontal lobe functions or functional neuroimaging studies are required to address this matter. In conclusion, WMH observed on MRI affects parkinsonian motor symptoms, particularly gait symptoms and levodopa-unresponsive bradykinesia symptoms.

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