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Differential Neuropsychological Profiles in Parkinsonian Patients With or Without Vascular Lesions

Gabriella Santangelo, PhD,[1,2,3] Carmine Vitale, MD, PhD,[1,3,4] Luigi Trojano, MD,[2]
Danilo De Gaspari, MS,[5] Leonilda Bilo, MD,[1] Angelo Antonini, MD,[5] and Paolo Barone, MD, PhD[1]*

[1]*Department of Neurological Sciences, University of Naples Federico II, Naples, Italy*
[2]*Neuropsychology Laboratory, Department of Psychology, Second University of Naples, Caserta, Italy*
[3]*Istituto di Diagnosi e Cura "Hermitage Capodimonte," Naples, Italy*
[4]*Faculty of Sciences of Movement, University of Naples, "Parthenope," Naples, Italy*
[5]*Parkinson Institute, Istituti Clinici do Perfezionamento, Milan, Italy*

Abstract: The purpose of this study is to compare the neuropsychological profile of patients affected by parkinsonism and vascular lesions to that in patients with PD alone (PD) and to evaluate whether the brain vascular lesion load is associated with neuropsychological variables. Thirty-six nondemented patients with parkinsonism were divided into 3 groups of 12 patients each, according to both clinical history and the presence of brain vascular lesions and/or dopaminergic denervation as revealed by magnetic resonance and dopamine transporter imaging, respectively. The first group had vascular lesions without dopaminergic denervation (VP group); the second group had vascular lesions and dopaminergic denervation (DD) (VP+DD group); and the third group consisted of patients with dopaminergic denervation (PD group) without vascular lesions. All patients underwent neurological and neuropsychological assessments. The groups differed in disease duration, age at onset, and cerebrovascular risk factors. The VP and VP+DD groups performed worse than the PD group on frontal/executive tasks. Regardless of the presence of dopaminergic denervation, cerebrovascular lesions in hemispheric white matter, basal ganglia, and cerebellum have an important effect in determining early onset and severity of cognitive impairment in patients with parkinsonism. © 2009 Movement Disorder Society

Key words: cerebrovascular lesions; dopaminergic denervation; cognitive functions; frontal lobe functions; Parkinson's disease

INTRODUCTION

In the absence of definite clinical diagnostic criteria, vascular parkinsonism (VP) is defined as a Parkinson syndrome occurring in cerebrovascular disease, after exclusion of Lewy body disease and other neurodegenerative conditions.[1–3] However, VP is difficult to distinguish from Parkinson's disease (PD), because basal ganglia infarcts can occur without parkinsonism,[4,5] and because a vascular disorder may occur in Lewy-body PD.[6]

Magnetic resonance imaging (MRI) studies[7,8] and a clinicopathological correlation study[2] suggested that two types of vascular lesions might cause VP, i.e., widespread, bilateral ischemic lesions and basal ganglia infarcts.

Also clinically, VP can be difficult to distinguish from PD, although recent studies have identified some clinical aspects that differentiate between the two diseases: primitive reflexes,[9] preserved olfactory function,[10] lower body parkinsonism,[11] postural instability, a history of stroke and risk factors for stroke, and failure to respond to levodopa (L-dopa) therapy.[8,12,13]

Previous studies reported that dementia[2] or cognitive impairment[2,8,13] were significantly more common in patients with VP than in patients with PD alone. In these studies, cognitive processes were not assessed by means of specific neuropsychological tasks, and the neuropsychological profile of patients with VP has yet to be fully

*Correspondence to: Dr. Paolo Barone, Department of Neurological Sciences, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy. E-mail: barone@unina.it

The first two authors contributed equally to this work.

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elucidated. The aim of our study was to evaluate the relevance of vascular lesions in determining cognitive impairment in patients with parkinsonism. To this aim, both frontal lobe functions and memory were assessed in three subpopulations of parkinsonian patients with: (a) dopamine denervation without vascular lesions; (b) vascular lesions without dopamine denervation; (c) both vascular lesions and dopamine denervation.

PATIENTS AND METHODS

Patients

We evaluated 36 patients with parkinsonism without dementia based on DSM IV criteria[14] and an age- and education-adjusted Mini-Mental State Examination (MMSE) score ≥ 23.8.[15,16] The diagnosis of parkinsonism was based on the presence of at least two of rest tremor, rigidity, postural instability, and bradykinesia. All patients underwent both brain MRI scan and [^{123}I] FP-CIT single-photon emission computed tomography (SPECT) of dopamine transporter ([^{123}I] FP-CIT-SPECT). They were divided into three groups according to clinical history and to the neuroimaging results. The first group consisted of 12 patients with parkinsonism of insidious onset, lacunar lesions on MRI, and normal [^{123}I] FP-CIT-SPECT imaging; these subjects were considered as a subset of patients with a diagnosis of vascular parkinsonism (VP group).[3] The second group consisted of 12 patients with parkinsonism of insidious onset, lacunar lesions on MRI, and abnormal [^{123}I] FP-CIT-SPECT imaging; these subjects were considered as a subset of patients affected by VP with nigrostriatal dopaminergic denervation (DD) (VP+DD group).[3,17] The third group consisted of 12 patients with probable idiopathic PD,[18] without lacunar lesions on MRI and with abnormal [^{123}I] FP-CIT-SPECT imaging (PD group).

MRI were obtained by 1.5T scanners. Axial (bicommissural plane), T2-weighted 5-mm thick fast-spin echo (TE from 80 to 120 ms), and axial FLAIR 5-mm-thick sections were rated by two experts, blinded to the patient's clinical condition. Vascular lesions in periventricular regions, hemispheric white matter, basal ganglia/thalamus, and brainstem/cerebellum were evaluated using the semiquantitative visual rating scale devised by Scheltens et al. (0–84 points).[19] The following items were assessed: periventricular hyperintensities, the number, size and locations of lesions in hemispheric white matter (frontal, parietal, occipital, and temporal lobes), basal ganglia (caudate, putamen and globus pallidus, thalamus, and internal capsule), and infratentorial foci (cerebellum, midbrain, pons, and medulla).

Dopamine transporter imaging was obtained by means of [^{123}I] FP-CIT SPECT. All images were visually evaluated by an experienced nuclear medicine doctor blind to patients' clinical condition and classified into normal and abnormal (unilateral, mild-to-moderate bilateral, severe bilateral) according to the current literature.[20]

Procedure

The assessment was performed in the morning, in a single session that lasted approximately 3 hours, with a break to avoid fatigue. Clinical, neuropsychiatric, and neuropsychological features were evaluated in all patients under medication. If the patients had motor fluctuations, all evaluations were made during the motor ON-phase before being tested; all patients gave their written informed consent to participate in the study.

Neurological Assessment

All patients with PD underwent a neurological examination by means of motor section of the Unified Parkinsons' Disease Rating Scale (UPDRS-section III)[21] and the Hoehn and Yahr scale[22] to measure severity of motor symptoms in "on" state. Furthermore, we recorded demographic details (age and educational level), neurological details, namely disease duration, age at PD onset, and type of onset (acute vs. subacute vs. insidious; symmetric vs. asymmetric), cerebrovascular risk factors, namely familiarity, hypertension (blood pressure > 140 mm Hg systolic and > 90 mm Hg diastolic), diabetes mellitus (fasting blood glucose level > 130 mg/dL), smoking (at least 20 cigarettes per day), hyperlipidemia (total cholesterol > 5.7 mmol/L), heart disease (coronary heart disease and cardiomyopathy), and hypotension (blood pressure < 90 mm Hg systolic and < 60 mm Hg diastolic). Total L-dopa equivalent daily dose (calculated as the sum of the L-dopa and DA agonists converted into L-dopa equivalent daily dose, LEDD) and chronic response to L-dopa (considered as sustained clinical improvement using at least 500 mg/day for at least 3 months) were recorded.

Neuropsychiatric Assessment

All patients underwent neuropsychiatric examination with: (1) the Hamilton Depression Rating Scale (HamD)[23,24] to measure the severity of depressive symp-

toms; and (2) the Neuropsychiatric Inventory (NPI)[25] to identify neuropsychiatric disturbances.

Neuropsychological Assessment

All 36 patients underwent standardized neuropsychological tasks to assess frontal lobe/executive functions and memory.

Frontal Lobe/Executive Functions

To evaluate frontal lobe functions, we used the Frontal Assessment Battery (FAB) screening instrument.[26] Specific frontal lobe functions were assessed as follows: (1) cognitive flexibility by means of the Phonological[27] and Semantic[28] verbal fluency tasks and the Wisconsin Card Sorting Test (WCST)[29,30]; (2) logical abstract thinking by means of Raven's Colored Progressive Matrices (RCPM)[27]; (3) spatial planning by means of copying task included in the Rey-Osterrieth Complex Figure Test (ROCF)[31] and the Clock Drawing Test (CDT)[32]; (4) set-shifting by means of the Trail Making Test (TMT),[33] a task consisting of two parts: part A (TMT-A) measures motor speed and visual research, and part B (TMT-B) provides a measure of frontal lobe functions. We considered the difference in score between TMT-A and TMT-B (TMT:B-A), a measure of set shifting; and (5) selective attention by means of Attentional Matrices, a cancellation task in which subjects are required to mark designated target number(s) within a 6×10 matrix filled with digits. Score range: 0 to 60.[28]

Memory

To evaluate the verbal long-term memory, we used the Rey auditory 15-word learning test[27] including immediate and delayed recall of word lists.

Statistical Analysis

Differences in the distribution of categorical variables among groups were assessed by means of χ^2 test. Group comparisons on demographic and clinical continuous variables were performed by means of analysis of variance (ANOVA). For the analysis of differences among groups on neuroradiological, neuropsychiatric, and neuropsychological variables, we adopted distribution-free nonparametric tests (Mann-Whitney *U*-test for comparing two samples, Kruskal-Wallis test for comparing three samples) to avoid biases due to the relatively small sample size. Moreover, to avoid type-I errors, we adopted a conservative statistical approach and applied Bonferroni's correction for the significance level ($P = 0.004$ for the neuropsychological tests; $P = 0.025$ for the neuropsychiatric data). The association between variables was assessed by the nonparametric Spearman correlation coefficient.

RESULTS

Clinical Results

Demographic and clinical findings are reported in Table 1. ANOVA showed no significant differences among the 3 groups of patients with respect to age, educational level, or severity of motor symptoms (UPDRS-section III and the Hoehn and Yahr scale). Patients of the PD group had a longer disease duration and a lower age at onset than patients with VP and patients with VP+DD. The type (symmetric vs. asymmetric and acute vs. subacute vs. insidious) of disease onset in patients of 3 groups was reported in Table 1. The prevalence of several cerebrovascular risk factors (heart disease, diabetes mellitus, hyperlipidemia, hypertension, and familiarity for vascular disease) significantly differed among the 3 groups (see Table 1).

With respect to antiparkinsonian treatment, the L-dopa equivalent daily dose did not differ among the 3 groups, but the response to chronic L-dopa did (Table 1). Neuroimaging results are reported in Table 2. With respect to vascular load, PD group had no lesion by definition; VP group presented more hyperintensities than VP+DD group in all studied brain regions, though differences between VP and VP+DD groups did not reach statistical significance (hemispheric white matter, $P = 0.244$; basal ganglia, $P = 0.800$; infratentorial foci, $P = 0.366$). Dopamine transport imaging identified both PD and VP+DD groups as having abnormal [^{123}I] FP-CIT SPECT. VP group was identified by normal [^{123}I] FP-CIT SPECT.

Neuropsychiatric and Neuropsychological Results

The behavioral and cognitive data of the 3 groups of patients are reported in Table 3. The results showed that Ham-D and NPI scores did not significantly differ among the 3 groups of patients.

Regarding neuropsychological scores, 4 patients (3 patients from the VP group and 1 patient from the VP+DD group) were excluded from the analysis because of missing data: 3 patients did not perform the TMT-B because of difficulty in recalling letters of the alphabet (due to low education level), while 1 did not perform the ROCF because of severe tremor. As shown in Table 3, significant differences among 3 groups

TABLE 1. *Demographic and clinical aspects of patients in the PD, VP, and VP+DD groups*

	PD group (n = 12)	VP group (n = 12)	VP+DD group (n = 12)	F	P
Characteristics					
Men/Women	11/1	9/3	8/4	2.250	0.325
Age (yr)	68.7 ± 6.9	72.2 ± 4.5	71.2 ± 4.9	1.303	0.285
Education (yr)	9.8 ± 4.2	7.3 ± 4.5	6.1 ± 3.4	2.629	0.087
Age at PD onset (yr)	57.8 ± 10.7	68.2 ± 5.6[a]	67.4 ± 4.6[a]	7.159	0.003
Acute/subacute/insidious onset	2/6/4	0/2/10	0/0/12	–	–
Symmetric/asymmetric onset	0/12	6/6	2/10	–	–
PD duration (yr)	10.7 ± 5.3	4 ± 2.8[a]	3.5 ± 1.2[a]	15.252	0.001
LEDD (mg/day)	680.2 ± 269.5	454.6 ± 290.5	462.5 ± 257.7	2.641	0.086
Hoehn and Yahr score	1.9 ± 0.6	2.3 ± 1.2	1.9 ± 0.6	0.560	0.577
UPDRS-III score in "on" state	16.7 ± 6.9	21.7 ± 9.1	24 ± 8.2	2.492	0.098
MMSE	27.8 ± 1.5	25.6 ± 3.6	25.5 ± 3.2	2.352	0.111
Response to chronic levodopa (no/yes)	0/12	12/0	2/10	–	–
Cerebrovascular risk factors				Chi-square	P
Hypertension (no/yes)	9/3	1/11	1/11	16.756	<0.001
Familiarity for vascular disease (no/yes)	12/0	3/9	2/10	20.285	<0.001
Hyperlipidemia (no/yes)	12/0	4/8	4/8	14.400	0.001
Heart disease (no/yes)	11/1	4/8	4/8	10.923	0.004
Smoking (no/yes)	11/1	9/3	8/4	2.250	0.325
Diabetes mellitus (no/yes)	12/0	7/5	9/3	6.107	0.047
Hypotension (no/yes)	12/0	12/0	12/0	–	–

Group comparisons on demographic and clinical continuous variables were performed by means of analysis of variance (ANOVA).
[a]Significantly different from the PD group on Bonferroni posthoc tests.
LEDD, levodopa dose equivalent; UPDRS-III score, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination.

were observed on the FAB and on semantic fluency task, whereas differences for phonological fluency task, RCPM, Attentive Matrices, and TMT-A did not reach the Bonferroni-corrected significance level. No significant difference among 3 groups of patients occurred on the remaining cognitive tasks. The Mann-Whitney *U*-test for comparing two samples showed that VP+DD patients performed worse than patients of the PD group on FAB, RCPM and Attentive Matrices, TMT-A, semantic fluency tasks. Moreover, patients with VP had significantly lower score than patients with PD on phonological and semantic fluency tasks and TMT-A. Further analysis did not show significant correlations between brain MRI load and neuropsychiatric or neuropsychological scores. Similarly, brain MRI load was unrelated to clinical data.

DISCUSSION

In this study, we compared the neuropsychological profile of patients affected by VP, PD, and VP+DD. Although patients with PD had an earlier onset and longer disease duration than patients with both VP and VP+DD, patients with vascular abnormalities (with or without concomitant dopaminergic denervation) had more severe frontal lobe dysfunctions as assessed by means of verbal fluency tasks than patients with PD alone. Furthermore, impairment of frontal lobe functions including cognitive flexibility, selective attention, and logical abstract thinking was more severe in patients with VP+DD than with PD.

Taken together, our neuropsychological findings indicate that vascular lesions are related to severe frontal lobe dysfunctions in patients with VP and patients with VP+DD, which is in line with previous neuropathological and neuroimaging studies.[7,8,34,35] Therefore, our data suggest that vascular lacunar infarcts in the deep white matter of the frontal lobe, caudate, or putamen may cause dysfunction of frontostriatal circuits and thus induce severe executive/frontal lobe dysfunctions. Although previous reports[36] in PD did not find significant relationships between cognitive altera-

TABLE 2. *Neuroimaging results in patients in the PD, VP, and VP+DD groups*

		PD group (n = 12)	VP group (n = 12)	VP+DD group (n = 12)
Vascular load	Hemispheric white matter hyperintensities	0	11.7 ± 8.4	7.7 ± 6.6
	Basal ganglia/thalamus hyperintensities	0	6.7 ± 5.7	5.9 ± 8.2
	Infratentorial foci of hyperintensities	0	1.4 ± 1.9	0.8 ± 0.8
DATSCAN	Subjects: normal/abnormal	0/12	12/0	0/12

The values of vascular load represented as mean ± standard deviation of semiquantitave visual rating scale.[19]

TABLE 3. *Behavioral and cognitive comparisons among the PD, VP, and VP+DD groups*

	PD group (n = 12)	VP group (n = 12)	VP+DD group (n = 12)	P
Neuropsychiatric parameters				
HAM-D	11.6 ± 6.9	12 ± 7.3	10.4 ± 6.7	0.397
NPI-12	14.2 ± 12.7	15.8 ± 14.1	15.7 ± 14.9	0.994
Neuropsychological parameters	PD group (n = 12)	VP group (n = 9)	VP+DD group (n = 11)	P
Frontal functions				
FAB	14.3 ± 2.3	12.7 ± 2.8	10.8 ±2.3[a]	0.003
Cognitive flexibility				
WCST-global score	48.2 ± 14.4	43.1 ± 18.1	43.1 ± 10.4	0.541
Phonological fluency	31.3 ± 10.8	19.9 ± 9.7	18.4 ± 8.6	0.005
Semantic fluency	16.5 ± 3.9	11.4 ± 3.4[a]	10.3 ± 4.1[a]	0.002
Logical abstract thinking				
RCPM	25.8 ± 4.3	24.2 ± 6.1	20.2 ± 4.1	0.023
Spatial planning				
ROCF-copy task	26.8 ± 5.9	25 ± 8.2	25.7 ± 7.5	0.690
CDT	6.8 ± 3	6.8 ± 3.7	5.4 ± 3.7	0.566
Set-shifting				
TMT-A	58.4 ± 27.8	93.6 ± 28.1	104.3 ± 66.9	0.011
TMT-B	181.9 ± 98.7	328.2 ± 204.5	322.6 ± 190.7	0.069
TMT: B-A	123.5 ± 97.6	234.7 ± 189.1	218.4 ± 139.1	0.183
Selective attention				
Attentive matrices	44.7 ± 13.7	43.8 ± 5.8	37.5 ± 7.8	0.043
Memory				
Immediate recall	42.2 ± 10.4	32.9 ± 6.4	35.4 ± 9.1	0.063
Delayed recall	8.6 ± 2.8	7.6 ± 2.8	7 ± 2.6	0.252

Group comparisons on neuropsychiatric and neuropsychological variables were performed by means of nonparametric tests (Kruskal-Wallis test for comparing the three samples). In case of statistically significant differences among the three groups (threshold for significance level was calculated $P < 0.004$ after Bonferroni correction), posthoc tests were performed by means of Mann-Whitney U-test for comparing two samples.

[a]Significantly different from PD.

HAM-D, Hamilton Depression Rating Scale; NPI, Neuropsychiatric Inventory; FAB, Frontal Assessment Battery; WCST, Wisconsin Card Sorting Test; RCPM, Raven's Colored Progressive Matrices; ROCF, Rey-Osterrieth Complex Figure Test; CDT, Clock Drawing Test; TMT, Trail Making Test.

tions and mild-to-moderate cerebrovascular lesions in PD, Jellinger[36] observed a significant increase of cognitive dysfunctions in patients with PD with severe cerebrovascular lesions pathologically proven. Similarly, we found more severe cognitive impairment in patients with cerebrovascular lesions (regardless of the presence of dopaminergic denervation) than in patients with PD alone. These data may indicate that extensive cerebrovascular lesions may have an important effect in determining severity and extent of cognitive dysfunctions as suggested previously.[36]

We found no significant correlations between vascular lesion load and cognitive scores. On the other hand, in 170 patients with mild cognitive impairment (MCI), a significant correlation was found between subcortical and periventricular white matter hyperintensities and executive dysfunctions.[37] This inconsistency might reflect either the different study population (PD vs. MCI) or the small sample size of our study. It is possible that the evaluation of interhemispheric differences might have revealed correlations between cognitive dysfunctions and vascular lesions. Unfortunately, the visual rating scale[19] used in our study does not evaluate such interhemispheric differences. Another limitation of this study is the lack of cortical damage and/or cortical atrophy evaluation.

In accordance with previous studies, we found that patients with VP and patients with VP+DD had more severe vascular risk factors (hypertension, familiarity for vascular disease, hyperlipidemia, heart disease, and diabetes mellitus),[1,8,12,13,34,38] an older age at onset, and a shorter duration of disease than patients with PD alone.[8,12,13,34,35,39,40] These data lend weight to Critchley's suggestion that a later onset age would favor a vascular cause.[1]

In line with earlier reports,[1,7,8,12,13,34,35,38,40,41] our patients with VP did not respond to treatment with L-dopa, whereas patients with PD alone did. Therefore, our results support the concept proposed by Zijlmans et al.[42] that a negative response to L-dopa in VP is related to the absence of macroscopic lesions in the basal ganglia and that VP might be associated with widespread frontal white matter lesions, relatively slight basal ganglia lesions, and good preservation of pigmented neurons in the substantia nigra. Moreover, 10 of 12 patients in our VP+DD group (83.3%) responded to L-dopa treatment, which indirectly supports the idea that a good response to L-dopa may be related to the pres-

ence of vascular and/or degenerative lesions predominating in or near the nigrostriatal pathway.[42]

Taken together, our findings suggest that cerebrovascular lesions especially in patients with PD may have an important effect in determining early onset and severe impairment of cognitive functions, mainly of frontal lobe functions. Therefore, in the clinical setting, besides assessing neurological status, the neurologist should also evaluate cognitive functions by means of a comprehensive neuropsychological examination in patients presenting suspected VP with and without degenerative PD.

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