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Evaluation Of Pharmacotherapy For The Patients With Depression In Alzheimer's Disease, Parkinson's Disease Or Vascular Dementia

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Abstract

Background: *Dementia has important clinical consequences for patients with PD and their caregivers, but the incidence is unknown.*
Objective: *This study was designed to investigate if there are possible distinctive features that might differentiate between cognitive decline direct consequence of Idiopathic PD and that of Alzheimer's type dementia associated with PD.*
Design: *This was a prospective, longitudinal cohort study.*
Methods: *There were six PD patients with dementia (3 male and 3 female), six matched PD patients without dementia (3 male and[1] 3 female) and six matched controls (3 male and 3 female) participated in this study. The patients were included from a large database of patients attending an out patients Parkinson clinic. All patients were treated with a combination of levodopa and variable doses of dopamine agonists but none were treated with antidepressants.*
Results: *The present findings showed that although patients with dementia performed worse than those without dementia on all neuropsychological tests, significant differences were found only on the semantic fluency test and Frontal assessment battery.*
Conclusions: *Patients with dementia were at a more advance clinical stage of Parkinson's disease and evidenced greater functional decline in comparison with patients without dementia*

Introduction

Dementia occurs commonly in PD, it may affect up to 75% of patients over the long term. To differentiate between PD with dementia and dementia with Lewy bodies, clinicians usually consider the timing of dementia onset. When dementia occurs within one year of the onset of Parkinsonism it is diagnosed as DLB, whereas PDD is diagnosed when dementia occurs after more than one year from the onset of Parkinsonism [1]. According to Rana, the prevalence of dementia in PD is about 19.7% in a survey of 310 patients. Furthermore, 90% were aged 70 or over, making age one of the most important risk factors of developing dementia [2]. A systematic review has shown that the prevalence of dementia

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in PD ranges from 24% to 31% [3]. A community-based study (4) examined the pattern of cognitive decline that may occur in 159 patients who were newly diagnosed as having PD. Cognitive features were assessed using the MMSE, the Pattern Recognition Memory Test (measuring temporal lobe function), the Spatial Recognition Memory Test (to assess both frontal and temporal lobes) and the Tower of London task (assessing planning and involving also working memory). The COWAT and other measures of verbal fluency have proven to be sensitive indicators of frontal lobe dysfunction. In 1989, Jerry Janowsky, Arthur Shimamura, and Larry Squire found that patients with circumscribed left or bilateral frontal lobe lesions produced significantly fewer words than did control subjects. Other researchers found that left frontal lesions resulted in lower word production than right frontal ones. Similarly, regional cerebral blood flow findings have shown left-sided frontal activation during the performance of verbal fluency tasks. Thirteen of the 159 patients scored below 24 on the MMSE, 30 patients scored below 16 on the recognition memory task and 14 patients who scored normally on the MMSE and recognition memory tasks performed poorly on the tower of London test, indicating that 57 out of the 159 patients studied (36%) had cognitive impairments. This study suggests that cognitive impairments occur even in newly diagnosed PD patients [4]. In addition, PD patients who participated in this latter study had re-assessment after three years, in order to detect any cognitive dysfunctions. Thirteen patients out of 126 had developed dementia (10%). Dementia was assessed by both MMSE and DSM-IV. A post-mortem study investigated the impact of co-existing AD pathology in PD patients with and without dementia [7]. This study examined 200 PD patients (mean age 77.0, range 58- 98) using The Consortium to Establish a Registry for Alzheimer's Disease as guidelines to rate co-existing AD pathology and the Braak staging of neuritic Alzheimer changes [8]. Presence of dementia was defined as a MMSE score lower than 20 and established following the DSM-III-R. In practice, patients had moderate to severe cognitive impairment. Patients' data were collected from the research files of Clinical Neurobiology in Vienna, Austria, from 1983-2000. The result showed that among the 200 patients, 66 (33%) were demented and 134 (67%) were not demented. In addition, 94% of patients diagnosed as demented had the cortical neuropathological changes of AD [7]. These findings indicated presence of dementia in PD patients also associated with AD type pathology. Several VBM studies have reported hippocampal atrophy in PDD subjects when compared with healthy control subjects [9,8,11]. Moreover, smaller hippocampal volumes have been found to be correlated with lower scores on the recognition memory task in PDD patients [10,12,13]. An MRI study reported a similar degree of medial temporal lobe atrophy in PDD, AD and DLB compared with control subjects [14]. These imaging findings support the idea that AD pathology contributes to abnormal cognitive decline in PDD patients. Some imaging studies have shown temporal and parietal lobe atrophy in PDD, similar to that seen in AD (15, 16). However, additional involvement of brain regions such as frontal and occipital lobe distinguishes brain atrophy due to PD from AD [16,17].

This study was designed to investigate if there are possible distinctive features that might differentiate between cognitive decline direct consequence of Idiopathic PD and that of Alzheimer's type dementia associated with PD.

Method

Sample

There were six PD patients with dementia (3 male and 3 female), six matched PD patients without dementia (3 male and 3 female) and six matched controls (3 male and 3 female) also participated in this study. The patients were included from a large database of patients attending an outpatients Parkinson clinic. The patients were diagnosed based on the UK PD Brain Bank Criteria (43). All patients had neuropsychological screening, neuropsychiatric assessment using the NPI, structural MRI scanning and neurological examination. According to Hoehn and Yahr stages (1967), all patients had mild PD. None

of the patients had a history of psychiatric disorders. All patients were treated with a combination of levodopa and variable doses of dopamine agonists, but none were treated with antidepressants. The PD patients were divided into two subgroups according to their MMSE above and below 24 score. The mean age of the PD patients with dementia was 67.67 years (SD= 11.2, range 49-80), their mean education was 8.5 years (SD= 5.65 range 5-18), their mean disease duration was 9.83 years (SD= 5.78) and their mean MMSE score was 20.5 (SD= 2.51 range 16- 24). The mean age of PD patients without dementia was 66.67 years (SD= 10.5, range 48-76), their mean education was 9.5 years (SD= 5.09 range 5-18), their mean disease duration was 8.33 years (SD= 8.31) and their mean MMSE score was 28.5 (SD= 1.97 range 26- 30). A group of healthy age matched controls was also included for comparison. The mean age of this healthy control sample was 69.50 years (SD= 12.34, range 56- 88), their mean education was 8.83 (SD= 4.96 range 4- 15) and their mean MMSE score was 28.83 (SD= 0.41 range 28- 29). None of the controls had a history of neurological or psychiatric diseases.

Task and Procedure

Data from a category fluency task were used for in depth assessment of lexical semantic characteristics. Each participant was asked to orally produce as many items as possible for each category (fruit and animal) within one minute. Performance was evaluated by calculating the total number of words produced by patients and controls in the two categories and by determining the lexical attributes (age of acquisition, familiarity, typicality and length) for each acceptable word. The data included in the analyses were the mean attributional values of the words produced by each patient and control.

Lexical Semantic Assessment

Age of Acquisition

Age of acquisition values for words were obtained by asking a sample of 46 healthy older adults (25 females, 21 males) mean age 68.87 (SD 7.68), mean education 9.76 9 (SD 5.09), mean MMSE 28.69 (SD 1.03) to rate the AOA of 289 words (66 fruit and 223 animal words) following the procedure reported in the study by Forbes-Mckay et al (2005). A random list of all 289 items was presented to each participant and asked to estimate the age (in years) at which they had learned each word. Harmonic mean AOA ratings for each item were calculated and used in the analyses. The raters were from a similar geographical and socio-cultural background as the patients and controls enrolled in this study. Ratings of AOA correlate highly with objective measures of AOA and therefore have good validity (44).

Typicality

Large numbers of reports have shown that access to semantic information such as picture identification and naming is effected by the typicality of category exemplars (45). The procedure for typicality was similar to that used for the AOA parameter. Raters (the same as in the AOA) were given a list of all items split into two categories (animal and fruit). They were asked to rate the typicality of each item by using a 7-point Likert type rating scale, from 7 (most typical) to 1 (least typical). Based on the instructions given by Larochelle, Richard, and Soulieres (2000), they were asked to rate how well each exemplar (e.g. apple) represented its specific category (e.g. fruit). Items were presented in random order to control for order effects (46).

Familiarity

Raters (the same as before) were given two separate list for animal and fruit categories. Then they were asked to rate the familiarity of each item, according to Likert type rating scale, from 7 (very familiar) to 1 (least familiar).

Length

Length was measured in terms of the number of letters in each word.

Statistical Analyses

An independent T-test and a series of independent T-tests were carried out to compare the demographic data and neuropsychological test scores of the two subgroups (PD patients with and without dementia). Further statistical analyses were also carried out to examine the relationship between MMSE scores and lexical-semantic test scores using Pearson's correlation test. To account for multiple comparisons, this study used a significance level of 0.004 for group comparisons among patients with and without dementia on the neuropsychological tests, and a significance level of 0.007 for group comparisons among both groups of patients on the MMSE and lexical-semantic test and for paired correlations, except for the group comparison of demographical data, for which the significance level was 0.01. In addition, Crawford & Garthwaite (2002) statistical methods were used to compare between patients with and without dementia (47). These methods have been used to compare an individual case with a small normative or control sample. The authors "provided significance tests and a point estimate of the abnormality of an individual's score. In addition, the work provides methods for obtaining confidence limits on the estimates of abnormality. It also extends the methods of obtaining point estimates to cover the case where an individual's score on each of k tests is compared with the individual's mean score on the k tests. That is, the method can now be applied to examining an individual's cognitive strengths and weaknesses across a set of measures" (48).

Results

Demographical data analyses

The first analysis was done using independent T-tests to compare demographic characteristics of PD patients with dementia and PD without dementia. There was no significant difference between the two groups of patients in age $t(10) = 0.160$, $p > .01$, gender $t(10) = 0.000$, $p > .01$, education $t(10) = -0.322$, $p > .01$ and duration of disease $t(10) = 0.363$, $p > .01$ (see Table 5.1)

Table 5.1 Mean (Standard Deviation), and P values scores of demographical data of PD patients with and without dementia.

	PD with dementia	**PD without dementia**	**P**
Age	67.67 (11.22)	66.67 (10.46)	0.876
Gender	1.50 (0.55)	1.50 (0.55)	1.000
Education	8.50 (5.65)	9.50 (5.09)	0.754
Duration of disease	9.83 (5.78)	8.33 (8.31)	0.724

Cognitive profile of PD patients with and without dementia

Independent T-tests were carried out on the scores from the neuropsychological tests in the battery to compare the cognitive performance of PD patients with dementia and PD patients without dementia. PD patients with dementia had lower scores on all neuropsychological measurements than PD patients without dementia. However, significant differences were detected in the Category fluency test $t(10) = -4.743$, $p < .004$ and Frontal Assessment Battery $t(6) = -5.667$, $p < 004$. There was no significant difference between the two groups of PD patients in the other neuropsychological tests, e.g. Letter fluency test $t(10) = -2.891$, $p > .004$, Similarities test $t(6) = -1.826$, $p > .004$, Digit span (forward) $t(10) = -1.859$, $p > .004$, Digit span (backward) $t(10) = -3.087$, $p > .004$, Visual-spatial span $t(6) = -1.477$, $p > .004$, Rey 15-word immediate recall $t(6) = -.079$, $p > .004$ and Rey 15-word delayed recall $t(6) = -.570$, $p > .004$ Table 5.2 gives an overview of the scores.

Table 5.2 Mean (Standard Deviation), and P values of scores on neuropsychological tests achieved by PD patients with and without dementia.

	PD with dementia	PD without dementia	P
Letter fluency test	15.00 (10.08)	29.33 (6.77)	0.016
Category fluency test	**14.83 (6.71)**	**39.17 (10.63)**	**0.001**
Similarities test	6.50 (0.71)	16.17 (4.58)	0.030
Frontal Assessment Battery	**7.50 (2.65)**	**16.00 (1.41)**	**0.001**
Digit span (forward)	4.60 (.55)	5.75 (1.26)	0.105
Digit span (backward)	2.60 (.55)	4.00 (.82)	0.018
Visual-spatial span	3.75 (.50)	4.75 (1.26)	0.190
Rey 15-word immediate recall	16.75 (10.99)	36.75 (15.44)	0.079
Rey 15-word delayed recall	5.00 (3.17)	6.50 (4.04)	0.589

Comparison between PD with and without dementia in the Lexical Semantic Assessment

The results of additional statistical analyses showed that there was no significant difference between PDD and PD without dementia in age of acquisition $t(10) = -0.128$, $p > .007$, familiarity $t(10) = -0.116$, $p > .007$, typicality $t(10) = -0.592$, $p > .007$, length of word $t(10) = 0.137$, $p > .007$ and number of error $t(10) = 0.397$, $p > .007$. However, there was a significant difference between the two groups of patients in MMSE $t(10) = -6.136$, $p < .007$, and number of words produced on the category fluency task $t(10) = -3.532$, $p < .007$ (See table 5.3).

Table 5.3 Mean (Standard Deviation), and P values of scores on MMSE and Lexical-Semantic Assessment of PD patients with and without dementia.

	PD with dementia	PD without dementia	P
AoA	5.29 (1.57)	5.39 (0.95)	0.901
Familiarity	4.40 (0.33)	4.44 (0.59)	0.910
Typicality	4.66 (0.23)	4.76 (0.39)	0.567
Length	5.65 (0.33)	5.62 (0.53)	0.894
error	2.00 (2.00)	1.50 (2.35)	0.699
Number of words	**15.83 (4.58)**	**28.67 (7.63)**	**0.005**
MMSE	**20.50 (2.51)**	**28.50 (1.97)**	**0.000**

Comparison of each demented patient with the total averages of all non-demented patients

Further analyses were carried out using the Crawford & Garthwaite (2002) statistical methods to compare each PD patient with dementia with the total averages of all PD patients without dementia. There was no significant difference between each PD patient with dementia and the PD patients without dementia in all lexical-semantic parameters except for one patient who showed a significant difference in AoA $p = 0.021$ (see Table 5.4).

Table 5.4 P values of each PD patient with dementia compared with the total averages of PD without dementia.

PD with dementia	AoA	Familiarity	Typicality	Length
Patient No. 1	0.246	0.497	0.486	0.211
Patient No. 2	**0.021**	0.265	0.163	0.382

Patient No. 3	0.136	0.322	0.497	0.445
Patient No. 4	0.354	0.388	0.429	0.424
Patient No. 5	0.341	0.338	0.251	0.220
Patient No. 6	0.116	0.278	0.326	0.445

Correlation analyses

Furthermore, correlation analyses were carried out with all PD patients and MMSE and Lexical-Semantic Assessment. There was no significant relationship between MMSE and number of words (r= .700, P > 0.007), age of acquisition (r= .103, P > 0.007), familiarity (r= -.022, P > 0.007), typicality (r= .065, P > 0.007), length of word (r= -.293, P > 0.007) and error (r= -.115, P > 0.007) (see table 5.5).

Table 5.5 Correlations between MMSE and Lexical-Semantic Assessment in PD patients

	MMSE	**Number of Words**	**AoA**	**Familiarity**	**Typicality**	**Length**	**Error**
MMSE	-	.700	.103	-.022	.065	-.293	-.115
Number of Words	.700	-	.401	-.089	-.050	.264	.081
AoA	.103	.401	-	-.746*	-.761*	.167	-.015
Familiarity	-.022	-.089	-.746*	-	.928*	.083	-.348
Typicality	.065	-.050	-.761*	.928*	-	.190	-.375
Length	-.293	.264	.167	.083	.190	-	.223
Error	-.115	.081	-.015	-.348	-.375	.223	-

*Value is significant at P < 0.007 (two-tailed).

Comparison between PD with dementia and healthy controls:

This analysis was done using independent T-tests to compare PD patients with dementia and healthy controls. There was no significant difference between the two groups in age t(10) = -0.269, p > .01, gender t(10) = 0.000, p > .01 and education t(10) = -0.109, p > .01 (see Table 5.6). The results of additional statistical analyses showed that there was a significant difference between PDD and healthy controls in familiarity t(10) = -8.630, p < .007, typicality t(10) = -4.892, p < .007, length of word t(10) = 9.748, p < .007, number of words t(10) = -5.974, p < .007, and MMSE t(10) = -8.027, p < .007. However, there was no significant difference between the two groups in age of acquisition t(10) = 2.827, p > .007 (See table 5.7).

Table 5.6 Mean (Standard Deviation), and P values scores of demographical data of PD patients with dementia and healthy controls.

	PD with dementia	**Healthy controls**	**P**
Age	67.67 (11.22)	69.50 (12.34)	0.793
Gender	1.50 (0.55)	1.50 (0.55)	1.000
Education	8.50 (5.65)	8.83 (4.96)	0.916

Table 5.7 Mean (Standard Deviation), and P values of scores on MMSE and Lexical-Semantic Assessment of PD patients with dementia and healthy controls.

	PD with dementia	Healthy controls	P
AoA	5.29 (1.57)	3.45 (0.28)	0.018
Familiarity	**4.40 (0.33)**	**6.22 (0.39)**	**0.000**
Typicality	**4.66 (0.23)**	**5.37 (0.27)**	**0.001**
Length	**5.65 (0.33)**	**4.08 (0.22)**	**0.000**
Number of words	**15.83 (4.58)**	**35.00 (6.39)**	**0.000**
MMSE	**20.50 (2.51)**	**28.83 (0.41)**	**0.000**

A further analysis was carried out using the Crawford & Garthwaite (2002) statistical methods to compare each PD patient with dementia and the total averages of all healthy controls. There was a significant difference between each PD patient with dementia and healthy controls in all lexical-semantic assessment except for one patient who showed no difference in AoA p = 0.069 and Typicality P = 0.112 (see Table 5.8).

Table 5.8 P values of each PD patient with dementia compared with total averages of healthy controls.

PD with dementia	AoA	Familiarity	Typicality	Length
Patient No. 1	**0.006**	**0.004**	**0.044**	**0.004**
Patient No. 2	**0.000**	**0.002**	**0.008**	**0.000**
Patient No. 3	**0.041**	**0.009**	**0.046**	**0.000**
Patient No. 4	**0.002**	**0.003**	**0.034**	**0.001**
Patient No. 5	**0.000**	**0.002**	**0.014**	**0.000**
Patient No. 6	0.069	**0.011**	0.112	**0.000**

5.1.3.7 Comparison between PD without dementia and healthy controls

This comparison was done using the independent T-test to compare PD patients without dementia and healthy controls. There was no significant difference between the two groups in age t(10) = 0.429, p > .01, gender t(10) = 0.000, p > .01 and education t(10) = -0.936, p > .01 (see Table 5.9). Moreover, the results of additional statistical tests showed that there was no significant difference between PD patients without dementia and healthy controls in typicality t(10) = 3.152, p > .007, MMSE t(10) = 0.405, p > .007 and number of words t(10) =1.559, p > .007. However, a significant difference was found in age of acquisition t(10) = -4.780, p < .007, familiarity t(10) = 6.165, p < .007 and length of word t(10) = -6.514, p < .007 (See table 5.10).

Table 5.9 Mean (Standard Deviation), and P values scores of demographical data of PD patients without dementia and healthy controls.

	PD without dementia	Healthy controls	P
Age	66.67 (10.46)	69.50 (12.34)	0.677
Gender	1.50 (0.55)	1.50 (0.55)	1.000
Education	9.50 (5.09)	8.83 (4.96)	0.823

Table 5.10 Mean (Standard Deviation), and P values of scores on MMSE and Lexical-Semantic Assessment of PD patients without dementia and healthy controls.

	PD without dementia	Healthy controls	P
AoA	**5.39 (0.95)**	**3.45 (0.28)**	**0.001**

Familiarity	**4.44 (0.59)**	**6.22 (0.39)**	**0.000**
Typicality	4.76 (0.39)	5.37 (0.27)	0.010
Length	**5.62 (0.53)**	**4.08 (0.22)**	**0.000**
Number of words	28.67 (7.63)	35.00 (6.39)	0.150
MMSE	28.50 (1.97)	28.83 (0.41)	0.694

A further analysis was carried out using the Crawford & Garthwaite (2002) statistical methods to compare each PD patient without dementia and the total averages of all healthy controls. There was a significant difference between each PD patient without dementia and healthy controls in all lexical-semantic assessment except for four patients who showed no difference in Typicality (see Table 5.11).

Table 5.11 P values of each PD patient without dementia compared with total averages of healthy controls.

PD with dementia	**AoA**	**Familiarity**	**Typicality**	**Length**
Patient No. 1	**0.006**	**0.011**	0.151	**0.000**
Patient No. 2	**0.000**	**0.001**	**0.005**	**0.000**
Patient No. 3	**0.000**	**0.002**	**0.011**	**0.023**
Patient No. 4	**0.002**	**0.004**	0.085	**0.000**
Patient No. 5	**0.018**	**0.015**	0.132	**0.001**
Patient No. 6	**0.000**	**0.012**	0.190	**0.000**

5.1.4 Discussion

This study is the first to investigate the properties and characteristics of the words generated in semantic fluency task by PD patients with and without dementia to see whether this method may discriminate between cognitive decline as a direct consequence of PD and that of Alzheimer's type dementia associated with PD.

The present findings showed that although patients with dementia performed worse than those without dementia on all neuropsychological tests, significant differences were found only on the semantic fluency test and Frontal assessment battery. These findings are in line with previous studies that found demented PD patients had impaired performance on the semantic fluency test (5, 34) and in executive function as assessed by the Frontal assessment battery (20, 21). The current results suggest that demented PD patients may have more impairment in semantic fluency than in phonemic fluency, which implies that those patients could have specific difficulties with the retrieval of semantic information.

Although the present findings could detect a significant difference between both groups of patients in the semantic fluency task, it could not identify significant differences between the two groups of patients on the properties and characteristics of the material recalled during the semantic task. This may be due to having a small sample size compared to the size of the effect expected between the two groups in the characteristics of the semantic fluency task in the current study.

Furthermore, the present findings showed that patients with dementia produced fewer words in the semantic fluency task than healthy controls did. The words generated by demented patients were longer, less familiar, less typical and acquired later in life than the words produced by healthy controls. Although the difference between these two groups in the AoA approached significance level, the result was not significant after applying a correction for multiple comparisons. Using a single case approach (as described in section 5.1.2.5, pages 212-213) showed a significant difference between each patient with dementia and the total average of all healthy controls in all lexical-semantic assessment features except for one patient who showed no difference in AoA and Typicality, confirming the

group comparison analyses. Surprisingly, the results of the single case analysis for patient with dementia compared with controls showed that 5 out of 6 patients differ significantly in AoA producing words that are acquired later in life. Apart from fewer words generated by PD patients with dementia, those patients interestingly showed completely different patterns in all characteristics of semantic fluency task compared with AD patients. This study suggests a new method could help differentiating between dementia caused by PD and AD type dementia in PD.

The present study also showed that non-demented patients generated words that were acquired later in life, were longer and less familiar than words produced by healthy controls. Therefore this implies that there is a similar pattern of lexical-semantic deficits underlying the fluency task performance in PD patients with and without dementia. Although the patients without dementia and healthy controls showed no significant difference in typicality scores, there was a significant difference between demented patients and healthy controls, suggesting that there might be some use for clinical application in differentiating between PD patients with and without dementia. The single case analysis (patients without dementia vs. healthy controls) confirms these suggestions in which four patients showed no difference in typicality scores.

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