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Prospective comparative study of the evolution of probable Alzheimer's disease and Parkinson's disease dementia

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Abstract

No previous comparison of test performance in probable Alzheimer's disease (pAD) and Parkinson's disease (PD) dementia has provided information about potential differences in the dementing process. This study compared the evolution of cognitive changes associated with these dementias. Generalized estimating equations (GEE) applied to regression analyses with repeated measures were used to evaluate cognitive changes over 1 to 3 years prior to the point when dementia was diagnosed in 40 matched pairs of patients with incident pAD and PD dementia. Both groups' performance declined on the Short Blessed, Selective Reminding Test (SRT; total recall, long-term retrieval, and delayed recall), Boston Naming Test, Category Fluency, and Similarities. The decline on naming and SRT delayed recall was more rapid in the PD dementia group, suggesting that these performance deficits emerge earlier in the development of pAD. The PD dementia group performed worse on Category Fluency throughout the follow-up period, suggesting either that dementia is overlaid on this preexisting performance deficit or that this type of executive deficit is an early manifestation of dementia in PD. The pAD group performed more poorly throughout the follow-up period on SRT delayed recognition, consistent with a pAD-specific encoding deficit. We conclude that while pAD and PD dementia are similar in many respects, differences in their evolution support previous observation of unique features in the 2 dementias and suggest different underlying pathologies. (JINS, 1998, 4, 279–284.)

Keywords: Alzheimer's disease, Parkinson's disease, Dementia, Prospective study

INTRODUCTION

There has long been an interest in comparing the cognitive features of probable Alzheimer's disease (pAD) and the dementia associated with Parkinson's disease (PD). The approach to this question that has been adopted by the majority of studies has been to match both groups on a global measure of dementia severity (such as a mental status test) and then to compare their performance on a battery of neuropsychological tests. This cross sectional approach has been used in many studies, and several review articles have summarized these findings (Dubois et al., 1991; Whitehouse, 1986). While these cross-sectional comparisons have been informative, they have not provided information about the dementing process; that is, the evolution of the cognitive

changes that precede dementia. Investigation of the dementing process can help elucidate clinical differences between the dementias. In some cases, dementia syndromes appear more similar once they are fully developed than during their evolution. Further, difference in the evolution of the cognitive changes in two dementing illnesses may provide information about the neuroanatomic substrates of the cognitive changes.

In the context of a prospective study of elders in the North Manhattan community, we have been following a cohort of nondemented elders with and without Parkinson's disease. A proportion of these elders have become demented during follow-up. In a previous study (Jacobs et al., 1995b), we attempted to find features of neuropsychological test performance in healthy, nondemented elders that would discriminate between those who did and did not become demented 2 years later. We reported that elders with "predementia" (i.e., those who would be diagnosed with dementia 2 years later) had poorer scores on tests of memory (either immediate or delayed recall) and naming. In a parallel study (Jacobs et al., 1995a), we evaluated the performance of nondemented PD patients who did and did not become demented 2 years later and found that the patients with predementia performed more poorly on verbal fluency tests. Taken together, these two studies suggested that features of neuropsychological test performance that were predictive of later dementia were different in pAD and PD dementia. This provided the impetus for our exploration of potential differences in the evolution of the two dementias.

In the present study, we focused only on elders who became demented. Our baseline for the analyses was the visit at which the patient became demented, and we then worked backward from this baseline, including as many of the individual's previous visits as were available. Using this approach our goals were (1) to compare pAD and PD dementia patients' test performance at the time of diagnosis, (2) to determine which tests revealed changes in performance as the patients demented, and (3) to determine if the rate of change in test performance over time differed in the two dementias.

METHODS

Research Participants

Participants included in these analyses were selected from those in a prospective, community-based study, the Washington Heights–Inwood Columbia Aging Project. To be considered for inclusion in the analyses they had to be diagnosed as nondemented at their initial visit and then diagnosed as demented at a subsequent visit. Two groups of incident dementia subjects were considered: those who developed pure pAD, and those who had PD at their baseline visit and then became demented (PDD). There were 47 patients with incident PDD and 121 with incident pAD. Our strategy was to match a pAD patient to each PDD patient for age at diagnosis of dementia, years of follow-up prior to the diagnosis of dementia, and years of education. This matching process produced 40 well-matched pairs of participants.

Procedures

All participants had the same standardized evaluation yearly. Evaluations were conducted in either English or Spanish, based on the participant's primary language and opinion of which language would yield better performance.

Neuropsychological evaluation

Participants received the following battery at each study visit:

1. Word list learning and memory: The Selective Reminding Test (SRT; Buschke & Fuld, 1974) was administered. Participants were given six trials to learn a list of 12 unrelated words. After each recall attempt, they were reminded only of those words that had not been suc-

- cessfully recalled. Two standard measures of immediate recall were calculated: total recall and long-term retrieval. Intrusions—words recalled that were not on the word list—were totaled. Delayed incidental free recall was assessed after a 15-min delay. A savings score was calculated as the percentage of words recalled on the sixth learning trial that were retained for delayed recall. Free recall was followed by a multiple-choice recognition task.
- Nonverbal memory: A multiple-choice version of the Benton Visual Retention Test (BVRT; Benton, 1955) was used to assess nonverbal memory. Participants viewed a geometric design for 10 s. It was then removed from view, and the participant was asked to recognize the design in a four-choice, multiple-choice array. Stimuli corresponded to Form D of the original Benton Visual Retention Test.
- 3. *Orientation*: The 10 orientation items from the Mini-Mental State Examination (Folstein et al., 1975) were used to assess orientation to time and place.
- Verbal reasoning: The Similarities subtest of the Wechsler Adult Intelligence Scale–Revised (Wechsler, 1981), which requires participants to identify relevant similarities or superordinate categories for paired items, was administered.
- 5. *Naming*: A 15-item version of the Boston Naming Test (Kaplan et al., 1983), a test of visual confrontation naming, was used to assess word-finding ability.
- 6. Letter fluency: We administered the Controlled Oral Word Association Test from the Multilingual Aphasia Examination (Benton & Hamsher, 1976). Different letters were used for Spanish and English-speaking subjects to control for word-frequency differences across the two languages as reported in the manual for the Multilingual Aphasia Examination (Benton & Hamsher, 1976).
- 7. *Category fluency*: All participants generated exemplars in the categories *animals*, *foods*, and *clothing*; 60 s was allowed for each category.
- 8. *Nonverbal reasoning*: The Identities and Oddities subtest of the Mattis Dementia Rating Scale (Mattis, 1976) was used to assess nonverbal reasoning.
- 9. Auditory comprehension: The first six items of the Complex Ideational Material subtest of the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983) were used to assess comprehension of spoken language.
- 10. *Repetition*: Participants were asked to repeat the high-frequency phrases from the Boston Diagnostic Aphasia Examination Repetition of Phrases subtest (Goodglass & Kaplan, 1983).
- 11. Visuoperceptual skills: Participants matched a target design to the same design presented simultaneously in a four-choice, multiple-choice array containing the target along with three distractors. Target stimuli corresponded to Form C of the original BVRT (Benton, 1955).

12. Visuoconstructional skills: Participants copied five designs from the Rosen Drawing Test (Rosen, 1981) ranging in difficulty from simple geometric shapes to overlapping, parallel, and three-dimensional figures.

Diagnostic evaluation

A neurologist elicited the medical—neurological history and conducted a standardized physical and neurological examination. All ancillary information, including medical charts and CT or MRI scan reports (if available), were included in the evaluation. The presence of a history or signs or symptoms of stroke was noted, as well as the presence of diabetes and hypertension. Idiopathic PD was defined by clinical and research criteria (Hughes et al., 1992a, 1992b; Ward & Gibb, 1990). Patients with secondary parkinsonism resulting from phenothiazines, alphamethyldopa, reserpine, or metaclopramide hydrochloride, and patients with clinical presentations suggesting progressive supranuclear palsy, essential tremor, Shy-Drager syndrome, presumed striatonigral degeneration, and olivopontocerebellar atrophy were excluded.

Separate from the neuropsychological testing, the neurologist administered the short version (Katzman et al., 1983) of the Blessed Memory Information and Concentration Test (Blessed et al., 1968) as well as assessments of functional capacity or activities of daily living including the Blessed Dementia Rating Scale (Part I, Sections A and B; Blessed et al., 1968). In assessing functional capacity, the physicians were careful to determine whether a functional problem could be based on physical disability alone. This consideration was important for determining the presence of functional changes in PD patients that were consistent with dementia.

Test scores from the neuropsychological battery were evaluated using a fixed paradigm (Stern et al., 1992): Criterion scores were applied to each test score, and patients performing below these scores on two out of three components of memory testing (immediate and delayed verbal, and immediate nonverbal) as well as two out of four other defined cognitive areas (orientation, language, abstract reasoning, or construction) were considered to have sufficient cognitive deficits to meet our criteria for dementia. These criterion scores did not vary as a function of age, education, or disease status (i.e., healthy elders or Parkinson's disease).

Information from these evaluations was presented at a diagnostic conference of physicians and neuropsychologists, and a consensus diagnosis was made. The diagnosis of dementia was based on Diagnostic and Statistical Manual (3rd Edition–Revised) criteria (American Psychiatric Association, 1987), and required evidence of cognitive deficit, based on the neuropsychological scores, as well as evidence of impairment in social or occupational function, based on the formal functional assessments, elicited history, or both. When applying the latter criterion, careful attention was given to the potential effect of the motor signs and symptoms of PD on functional capacity.

When dementia was diagnosed, all available data were evaluated to determine the type of dementia present. The diagnosis of pAD was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA; McKhann et al., 1984). Although the NINCDS–ADRDA criteria were not designed for patients with Parkinson's disease, they describe a systematic approach towards ruling out potential causes of dementia such as stroke or vitamin deficiency. We applied this same approach to the patients with PDD in order to rule out other potential causes of dementia.

Statistical analysis

Analysis focused on a subset of tests and test scores from the diagnostic neuropsychological evaluation. These were selected for their potential to discriminate between the two dementing processes based on previous comparisons (Jacobs et al., 1995a, 1995b; Stern et al., 1993). Tests evaluated included (1) Boston Naming Test (15-item version), total score; (2) Controlled Oral Word Association Test (COWAT), mean of 3 letters; (3) Category Fluency, mean of 3 categories; (4) WAIS–R Similarities, scaled score; (5) Selective Reminding Test, total recall, long-term retrieval, savings (percent of words recalled on last trial that are recalled at 15-min delayed recall), delayed recognition, intrusions; (6) Benton Visual Retention Test (multiple choice version), recognition; and (7) Rosen Drawing Test (fiveitem version), total score. In addition we evaluated change in the total score Short Blessed Memory Information Concentration Test that was administered by the physician.

The analytic strategy was to compare progression of neuropsychological test performance over time in the pAD and PDD patients. Since we were interested in performance changes that resulted in dementia, the time frame for the analysis was the reverse of the standard repeated measures analysis. The baseline was the visit at which dementia was diagnosed, and we evaluated change from this baseline in the years prior to the diagnosis. Thus, Year Zero was the visit at which the diagnosis was made, Year 1 was the visit prior to that, and so on, back to a maximum of three previous visits. The actual number of visits available for analysis differed across patients.

Analyses of the longitudinal data were performed by applying generalized estimating equations (GEE) to regression analyses with repeated measures (Liang & Zeger, 1986). This statistical method takes into account the multiple visits per participant and the fact that the characteristics of a single individual over time are likely to be correlated with one another. The repeated measures for each participant (up to four per variable) are treated as a cluster. A second advantage of GEE is that it takes into account the status or changing value of each covariate at each visit. Tabled values for regression analyses involving the factor scores are regression coefficients and their standard error (Table 2).

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We examined test performance over time as a function of disease group (pAD vs. PDD). All analyses controlled for age at diagnosis of dementia and years of education to adjust for any residual imbalances after the matching process and within-group effects of these variables. In a supplementary analysis, we also included the language each participant was tested in as a covariate. The regression models provided estimates of the association of neuropsychological test scores with group, follow-up time and the interaction of Group × Time. A significant group effect indicates a difference between the two groups at the time when dementia was diagnosed, with a negative value indicating that the PDD group performed worse than the pAD group. A significant time effect indicates significant change in test scores over time, with a positive value indicating a decrease in test scores from initial testing to the time when dementia was diagnosed. Because of the structure of the GEE model, the coefficient for the time effect represents the slope of the change of the score over time in the pAD group. A significant interaction of Group × Time indicates differential rates of change in a test score as a function of group, with value of the coefficient representing the difference between the two groups' slopes. A positive value indicates greater change over time in the PD group.

RESULTS

Demographics

The pAD and PDD participants were well matched for age at the diagnosis of dementia, years of follow-up prior to the diagnosis of dementia, and education (Table 1). They did not differ significantly in the language they were tested in, or in severity of dementia at the time of diagnosis as assessed by the short Blessed test. There were significantly more women in the pAD group

All participants were seen 1 year prior to the visit at which dementia was diagnosed. In the pAD group, 27 patients were also seen 2 years, and 6 patients 3 years prior to diagnosis

Table 1. Demographics of 80 patients with incident dementia during follow-up^a

Variable	PDD (N = 40)	pAD (N = 40)
Age ^b (years; M, SD)	79.5 (6.7)	79.3 (5.9)
Education (years; M, SD)	9.2 (4.0)	9.2 (4.1)
Number of yearly visits (M, SD)	1.5 (0.5)	1.6 (0.5)
Short Blessed Test ^b (score; <i>M</i> , <i>SD</i>)	10.5 (6.7)	10.7 (4.7)
Female (%)	50	72.5*
Tested in English (%)	70	57.5

^{*}p < .05

of dementia. In the PDD group, 21 patients were also seen 2 years, and 11 patients 3 years prior to the diagnosis of dementia,

Prospective Analyses

Results of the GEE analyses are summarized in Table 2. For several tests the age at which the patient became demented and education contributed significantly to the models, indicating that performance on those tests varies as a function of age or education.

Group Differences

At the time that dementia was diagnosed, performance did not differ significantly between the two groups (i.e., there was no significant group effect) for all tests but two: Category Fluency and SRT delayed recognition. As indicated in the table footnotes, the direction of the group differences can be determined by the sign of the regression coefficient. For Category Fluency, the PDD group performed significantly worse at the time that dementia was diagnosed. For SRT delayed recognition, the pAD group performed worse.

Change Over Time

There was a significant time effect for the following tests: the short Blessed, Boston Naming, Category Fluency, Similarities, and SRT (total recall, long-term retrieval and delayed recall subtests; see Table 2). As would be expected, in each case there was a decline in performance from the initial visit to the time when the patient became demented. Note that for the short Blessed higher scores indicate worse performance, accounting for the opposite sign on the regression coefficient associated with that test. The time effect was not significant for the COWAT or the Benton Recognition Test.

Group Differences in Rate of Change

For all but two tests, the Group \times Time interaction was not significant, indicating that the rate of decline was similar in both groups. There were significant Group \times Time interactions for the Boston Naming test and for SRT delayed recall. In each case, the regression coefficients indicate that the PDD group's performance declined more rapidly over time.

Language of Test Administration

In a supplementary analysis, we also included the language the participant was tested in as an additional covariate in the GEE analyses. In no case did the addition of that covariate change the findings with regard to the group, time, or Group \times Time interaction effects.

DISCUSSION

As might be expected in prospective follow-up of participants who became demented, scores on most tests declined

^aParticipant groups were pairwise matched for age at diagnosis of dementia, years of follow-up at the diagnosis of dementia, and years of education.

^bAt the time that dementia was diagnosed.

Table 2. Regression coefficients (and their standard errors) in the regression models

Variables	Dementia age	Education	Group ^a	Time ^b	$Group \times Time^c$
Short Blessed	-0.046 (0.071)	-0.284 (0.133)*	-0.299 (1.381)	-3.674 (1.482)*	-1.028 (0.956)
Boston Naming	-0.019(0.044)	0.082 (0.060)	-0.719(0.537)	1.312 (0.564)*	0.823 (0.337)*
COWAT	0.058 (0.042)	0.268 (0.057)*	-0.323(0.579)	0.778 (0.604)	-0.078(0.355)
Category Fluency	-0.034(0.042)	-0.137 (0.055)*	-1.787 (0.625)*	1.893 (0.708)*	0.424 (0.438)
Similarities	0.002 (0.025)	0.198 (0.042)*	-0.453(0.411)	1.081 (0.385)*	0.429 (0.280)
SRT, total recall	-0.095(0.073)	0.073 (0.142)	-0.264(1.307)	5.265 (1.435)*	0.419 (0.917)
SRT, long-term retrieval	-0.135 (0.072)**	-0.27 (0.134)	-1.736(1.180)	4.327 (1.584)*	0.879 (1.021)
SRT, delayed recall	-0.017(0.026)	-0.003 (0.038)	-0.050(0.338)	1.884 (0.459)*	0.868 (0.299)*
SRT, savings	-0.031 (0.011)*	0.0189 (0.015)	0.128 (0.115)	0.043 (0.187)	0.014 (0.141)
SRT, delayed recognition	-0.001(0.027)	0.047 (0.043)	1.042 (0.485)*	0.815 (0.453)**	-0.379(0.300)
SRT, intrusions	-0.019(0.025)	0.024 (0.043)	-0.341(0.527)	-0.853(0.587)	-0.310(0.409)
Benton Recognition	-0.002(0.027)	0.086 (0.037)*	0.083 (0.397)	0.846 (0.569)	0.155 (0.350)
Rosen, total score	0.122 (0.014)	0.074 (0.021)*	-0.254 (0.219)	0.549 (0.312)**	0.169 (0.201)

^{*}p < .05, **p < .01.

significantly over time. At the time that dementia was diagnosed, test performance was comparable in the two groups for all but two tests. Also, for all but two of the neuropsychological tests considered, the rate of decline due to dementia was comparable in patients with PDD and pAD. Since the focus of many studies has been to elucidate differences between these two dementias, it is important to note the extent of their similarity, both in their presentation cross-sectionally and in their evolution.

Despite high degree of similarity of the two dementias, differences emerged on a subset of tests. At the time that dementia was diagnosed, PDD patients performed more poorly on category naming and pAD patients on delayed recognition. Since there was no significant interaction effect for these tests (and thus their rate of change was comparable in the pAD and PDD groups), it can be concluded that these performance differences remained constant throughout the follow-up period. Also, the PDD patients had a more rapid rate of decline on naming and delayed recall. Since the two groups' performance on these two tests was equivalent at the time that dementia was diagnosed, it can be concluded that, at the beginning of the follow-up period, the PD groups' performance was better than that of the group that developed pAD.

These results are compatible with previous cross-sectional analyses comparing pAD and PDD. The consensus of previous studies has been that while the two dementias are quite similar, some differences can be noted in their performance profile, most notably: (1) patients with PDD have better recognition memory that those with pAD, despite their equally impaired recall (Helkala et al., 1988; Stern et al., 1993); (2) the rate of forgetting from immediate to delayed recall is slower in PDD than in pAD (Troster et al., 1993); and (3) patients with PDD tend to perform worse on tests of verbal fluency (Bayles et al., 1993; Stern et al., 1993).

The present study is compatible with our findings in a previous cross-sectional study (Stern et al., 1993), where

we compared test performance of two sets of PD and pAD patients, each matched for overall intellectual function using a mental status test: a set of PDD and pAD patients as well as a set of nondemented PD and mild pAD patients. Our current findings suggest that prior to the onset of dementia PD patients' delayed memory and naming performance is better than elders with "pre-pAD." In the cross-sectional study, delayed recall was poorer in pAD patients than in nondemented PD patients, but delayed recall was comparable in the set of pAD and PDD patients. Similarly, in the Jacobs et al. studies reviewed above, poorer memory (either immediate or delayed recall) and naming scores could be used to identify nondemented individuals who would develop pAD (Jacobs et al., 1995b), while other tests were predictive of PDD (Jacobs et al., 1995a). Thus, while delayed recall and naming deficits emerge early in pAD, they are not a prominent feature of the cognitive changes seen in nondemented PD patients and evolve only as the patient becomes demented. This may suggest that there is a discontinuity between cognitive changes seen in nondemented and demented PD patients. Therefore, dementia in PD may represent a separate neuropathologic process from that causing the earlier cognitive changes.

Even when dementia was diagnosed, the PDD group performed better than the pAD group on delayed recognition. This observation is consonant with our cross-sectional study (1993) as well as other studies demonstrating that recall deficits are comparable in pAD and PDD, while recognition memory is more preserved in PDD (Helkala et al., 1988). It has been suggested that this represents a pAD-specific encoding deficit, such that PD dementia patients encode the material to the degree required for later recognition, while patients with pAD do not.

In the current study, the PDD group performed more poorly than the pAD group on verbal fluency throughout the course of follow-up. Similarly, in our cross-sectional study, nondemented and demented PD patients performed

^aPositive value indicates PDD group performs better than pAD group at time of dementia diagnosis.

^bPositive value indicates decline in test score as patient dements.

^cPositive value indicates greater change over time in the PDD group than the pAD group.

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worse than their respective pAD comparison groups on verbal fluency and visuospatial tasks. This may suggest that when dementia occurs in PD it is overlaid on cognitive changes that already exist in nondemented patients such as verbal fluency deficits. However, Jacobs et al. (1995a) observed that low verbal fluency scores were predictive of later dementia in PD. In addition, it has been suggested that executive dysfunction is associated with increased risk of developing PDD (Piccirilli et al., 1989). Our present observations cannot differentiate between these two possibilities, but the high prevalence of executive dysfunction in PD argues against the idea that it is simply an early manifestation of dementia.

In summary, while pAD and PD dementia are similar in may respects, their evolution differs in important ways. These differences support previous observations of unique features in the two dementias and suggest different underlying pathologies.

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