Educational Level as a Modulator of Cognitive Performance and Neuropsychyatric Features in Parkinson Disease

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Objectives: To test a possible association between the educational level (EL), cognitive performance, and neuropsychiatric features in Parkinson disease (PD).

Background: An inverse association has been reported between EL and cognitive dysfunction in patients with senile dementia of Alzheimer type but it is yet unsettled whether education has a similar effect on cognition in PD.

Methods: Seventy-two PD patients (45 males, mean age 68.7 ± 11.6 y) underwent a detailed neurologic examination, a battery of neuropsychologic tests, and questionnaires for the evaluation of psychosis, sleep disturbances, and depression. According to the number of educational years, patients were divided into 3 groups: low EL (0 to 8 y), (15 patients), intermediate EL (9 to 12 y) (28 patients), and high EL ($\geq$ 13 y) (29 patients).

Results: Patients with a higher EL had a better cognitive function and an association was found between the patients' EL and their scores in various neuropsychologic tests mainly those sensitive to frontal lobe dysfunction. Low education was associated with an increased risk for hallucinations and a trend for more depression, delusions, and sleep disturbances.

Conclusions: The association between high educational attainment and the lower risk of cognitive dysfunction suggest that education might modulate cognitive performance in PD.

Key Words: Parkinson disease, education, cognitive performance, neuropsychyatric features

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Patients with Parkinson disease (PD) commonly develop cognitive impairment, mainly in domains of executive functions, visuospatial orientation, and memory.[1,2] Progression to an overt dementia occurs in 15% to 44% of cases.[3,4] Other nonmotor symptoms such as sleep disturbances and a variety of neuropsychiatric manifestations including depression, behavioral changes, and psychosis may also develop.[5]

An inverse association has been demonstrated between educational level (EL) and of cognitive dysfunction in patients with Alzheimer disease (AD)[6] and in elderly nondemented individuals,[7] but it is yet unsettled whether education has a similar effect on cognitive performance and the risk for dementia in PD. Few studies suggested that there might be a protective effect of high EL on cognitive decline in PD[8–11] whereas others did not.[12] The effect of a prior EL on the chance of developing other neuropsychiatric complications such as psychosis and depression has not been studied yet. This prompted us to conduct a study evaluating the possible association between the EL and cognitive functions, depression, and psychosis in PD.

METHODS

Subjects

Consecutive patients with idiopathic PD were prospectively recruited between September 2003 and January 2004 from the Movement Disorders Clinic and the Neurology Service at Sheba Medical center. Diagnosis was made in accordance with the UK Brain Bank Criteria.[13] Patients were excluded if they had another central nervous system disorder (eg, normal pressure hydrocephalus, stroke), a concomitant primary psychiatric disorder, an end stage state (dementia or parkinsonism), or previous functional neurosurgical procedure or head trauma.

Clinical Assessment

Upon approval by the Institutional Review Board and signing an informed consent, patients underwent an interview-based assessment of demographic and clinical data followed by a detailed neurologic examination including Unified Parkinson's Disease Rating Scale (UPDRS)[14] and the Hoehn and Yahr Staging.[15]

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Level of Education

The number of years of education was reported by the patients and confirmed by their relatives. On the basis of the structure of the Israeli educational system patients were divided into 3 groups. The low EL included patients with partial or complete elementary school education (0 to 8 y of education). The intermediate EL consisted of patients with partial or complete high-school education (9 to 12 educational years). Patients with partial or complete university or college education (above 13 educational years) were included in the high EL group.

Neuropsychologic and Neurobehavioral Assessment

A trained psychologist administered the questionnaires and semiquantitative tests for the evaluation of cognition, sleep disturbances, psychosis, and depression. The global cognitive functioning was assessed using the Mini-Mental State Examination (MME),[16] the Frontal Assessment Battery (FAB),[17] the Rey-Osterrieth Complex Figure test (RCFC), including copy, immediate, and delayed tests, the Hebrew version of Rey-Auditory Verbal Learning Test (AVLT),[18] digit span forward and backward,[19] trail making A and B, the tower of Hanoi puzzle, phonemic and semantic word fluency, and the number cancellation test.[20] Depression was evaluated by UPRDS item 3 and by the Beck Depression Inventory (BDI).[21] The presence of hallucinations, delusions, and sleep disturbances was assessed in an interview and by UPDRS items 2 and 41, respectively.

Statistical Analysis

All analyses were performed using SAS statistical software version 8.2 (SAS Institute). To determine the significance of the differences between proportions and means, χ^2 and analysis of variance's (ANOVA) tests, respectively, were used. Continuous variables are expressed as mean ± 1 SD. Two-sided probability values are reported. Logistic multivariate regressions were performed to assess the relationship between level of education and the following binary variables: hallucination, delusion, depression, sleep disturbance, and BDI. Education was entered as 2 dummies variables, with high education as the reference group. For the continuous and ordinal variables a 1-way ANOVA was used to test the differences in the means of the groups of level education. Both logistic and ANOVA's analyses were adjusted for the following covariates: age, disease duration, and disease severity. P value < 0.05 was considered significant, with a Bonferroni correction for multiple comparisons.

RESULTS

Patient's Characteristics

Seventy-two patients with PD (45 males and 27 females) were recruited. Their mean age was 68.7 ± 11.6 years (range: 42 to 96 y) and mean disease duration 7 ± 4.7 years (range: 0.5 to 18 y). The average number of years of education was 11.9 ± 3.7 (range 0 to 19). Patients were divided into 3 groups according to the reported formal years of education. Fifteen patients had low EL (0 to 8 y, mean 6.5 ± 2.2 y), 28 patients had intermediate EL (9 to 12 y, mean 11.1 ± 1.1 y), and 29 patients had high EL ($\geq$ 13 y, mean 15.5 ± 1.2 y).

Comparison of the 3 groups (Table 1) showed that patients in the high EL group were significantly younger than patients in the 2 other groups. The age of onset also varied between the groups in accordance with the younger age of the patients in the high EL group. Male to female ratio were also different between this group and the former 2 but the difference was not statistically significant. No difference was evident between the groups in terms of disease duration and disease severity. Therefore, the rest of group analysis was adjusted according to age.

Performance of the 3 Educational Groups on Neuropsychologic Tests

As can be seen in Table 2, when comparing the performance on neuropsychologic testing significant differences between the educational groups were apparent. The effect of education persisted after a regression model adjusting for age, disease duration, and disease severity. Most cases in which the groups' performance was different it was attributed to better performance in the high EL group over the other 2 groups. Verbal memory, as measured with the Rey Auditory Verbal

TABLE 1. Patients' Characteristics

	Low EL	Intermediate EL	High EL	*P*
Number	15	28	29	—
Age (y)	75.73 ± 6.3	71.04 ± 9.6	62.97 ± 12.9	0.001*
Age of onset (y)	67.8 ± 8.91	64.82 ± 10.18	56.41 ± 14.78	0.005
Disease duration (y)	9.93 ± 5.05	8.21 ± 3.71	8.55 ± 5.34	0.511
Men	8 (53.3%)	15 (53.6%)	22 (75.9%)	0.157
H&Y > 2	5 (33.3%)	6 (21.4%)	8 (27.6%)	0.688

*Statistically significant ($P < 0.05$).

Values for age, age of onset, and disease duration are means ± standard deviation.

Men, the number (and percentage) of men; H&Y > 2, The number (and percentage) of patients with Hoehn and Yahr score larger than 2.

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TABLE 2. Patient's Performance in Neuropsychologic Tests

Item	Low EL	Intermediate EL	High EL	P*	Post Hoc Comparisons
No. patients	15	28	29	—	—
MME	23.7 ± 4.5	25.5 ± 3.2	27.8 ± 1.7	0.0255†	L = I < H
FAB	10.9 ± 3.8	13.6 ± 2.8	15.8 ± 2.3	0.0005†	L < I < H
RCF Copy	24.4 ± 8.3	28.7 ± 7.6	31.5 ± 6.3	0.2969	—
RCF Immediate recall	7.8 ± 6.7	13.1 ± 8.4	13.1 ± 8.3	0.3312	—
RCF Delayed recall	9.7 ± 7.5	13.2 ± 8.5	15.0 ± 7.4	0.6550	—
Rey AVLT Trial 1	3.5 ± 2.0	3.7 ± 1.9	5.5 ± 2.6	0.0251†	L = I < H
Rey AVLT Trial 5	7.4 ± 3.6	7.4 ± 2.3	11.4 ± 2.5	0.0002†	L = I < H
Rey AVLT Trial 8	6.8 ± 4.1	5.9 ± 2.9	9.5 ± 3.5	0.0121†	L = I L = H I < H
Digit Forward	7.9 ± 2.0	6.9 ± 2.4	8.5 ± 2.3	0.0942	—
Digit Backward	3.8 ± 1.9	4.8 ± 1.9	6.7 ± 2.6	0.0297†	L = I < H
Phonemic word fluency	4.7 ± 2.3	6.9 ± 3.0	9.0 ± 2.9	0.0037†	L = I, I = H, L < H
Semantic word fluency	11.2 ± 6.5	11.6 ± 5.2	17.5 ± 4.9	0.0118†	L = I < H
TOH time	13.6 ± 4.2	14.7 ± 7.7	9.2 ± 3.9	0.5879	—
TOH moves	36.7 ± 19.2	33.4 ± 18.2	40.1 ± 17.3	0.7142	—
No. canceling test 1	208.5 ± 90.6	160.3 ± 67.0	116.4 ± 47.8	0.0476†	L = I I = H L < H
No. canceling test 2	197 ± 79	163 ± 51	131 ± 46	0.2011	—
Trail Making A	264.3 ± 219.5	123.4 ± 78.6	74.1 ± 48.0	0.0019†	L = I > H
Trail Making B	292.0 ± 161.6	299.3 ± 173.9	182.5 ± 122.5	0.2786	—

*ANOVA, Adjusted for age, disease duration, and disease severity (UPDRS).
†Statistically significant ($P < 0.05$).
Values are mean score ± standard deviation.
H, high educational level; I, Intermediate educational level; L, low educational level; number of canceling test 1, 1 digit cancellation (8); number of canceling test 2, 2 digits cancellation (5 and 3); Rey AVLT Trial 1, Rey Auditory Verbal Learning Test: Immediate recall; Rey AVLT Trial 5, Rey Auditory Verbal Learning Test: Learning; Rey AVLT Trial 8, Rey Auditory Verbal Learning Test: Twenty minutes Delayed Recall; TOH time, The Tower of Hanoi Puzzle: Time to solution; TOH alm, The Tower of Hanoi Puzzle: number of moves to solution.

Learning Test (Rey AVLT), was more sensitive to EL than visual memory as measured by the RCFC. Quite consistently, the frontal lobe tests were sensitive to EL.

Association Between Education and the Prevalence of Neuropsychiatric Features

Patients with low and intermediate level of education had more hallucinations when compared with patients with high levels of education (26.7%, 35.7%, and 3.4%, respectively). Odds ratio calculation revealed that patients with low and intermediate level of education are at increased risk of developing hallucinations although the difference was statistically significant only between the intermediate and high EL groups (Table 3). The differences between the groups could not be attributed to the use of levodopa or dopamine agonists (actually the mean dose of DA agonists was significantly lower in patients in the low and intermediate EL groups) and persisted after adjustment to age and dosage of levodopa and its equivalents. When compared with the highly educated group those patients tended to suffer more from delusions, depression, and sleep disturbances but this did not reach a statistical significance.

DISCUSSION

In our sample of PD patients, an analysis showed that high educational attainment was associated with a lower risk of cognitive dysfunction. Low education was associated with an increased risk for hallucinations

TABLE 3. The Effect of Education on the Prevalence of Neuropsychiatric Complications

	Level of Education	Odds Ratio (95% Confidence Interval)†	P
Hallucinations	Low vs. high	4.821 (0.382-60.891)	0.2241
	Intermediate vs. high	12.145 (1.259-117.140)	0.0308*
Delusions	Low vs. high	4.0 (0.3-51.1)	0.29
	Intermediate vs. high	7.7 (0.8-79.9)	0.09
Depression	Low vs. high	2.617 (0.574-11.924)	0.2137
	Intermediate vs. high	1.917 (0.559-6.575)	0.3008
BDI score < 12	Low vs. high	4.016 (0.692-23.314)	0.1214
	Intermediate vs. high	1.480 (0.394-5.565)	0.5620
Sleep disturbances	Low vs. high	2.542 (0.499-12.943)	0.2614
	Intermediate vs. high	1.563 (0.442-5.529)	0.4885

*Statistically significant ($P < 0.05$).
†Odds ratios are adjusted for age and dosage of levodopa and its equivalents.

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and a trend for more depression, delusions, and sleep disturbances.

Our results reinforce previous reports of a poorer performance on multiple neuropsychologic measures in less educated PD patients[8] and of an association between dementia and low educational attainment.[9,10] Our study is unique, however, by showing the specific domains that are affected by education and by the finding that education might have an effect on the risk of having neuropsychiatric complications like hallucinations and other disturbances.

In most cognitive measures for which education had a significant effect, the difference was driven by significantly better performance in the high education grouping comparison to the other 2 levels. In several cases the score differed only between the low and high education levels, and in only 1 case (ie, FAB) was the test sensitive to differences in performance at each EL. When the test was less sensitive (eg, word fluency) the difference was between the 2 extremes. In other words, the major step in terms of the effect of education on cognitive performance in PD patients was the transfer between high school and university.

Concerning the various cognitive domains it was evident that tests which are sensitive to executive functions (FAB, Digit backward, phonemic word fluency, semantic word fluency, and the simple trail making) were also found to be associated with education level. The exceptions were the tower of Hanoi puzzle (although in the mean time for solution there was a definite tendency toward significance $P < 0.061$) and the more complex trail making test (B) (although the absolute scores show a dramatic decrease of the performance time in the highly educated individuals comparing to the other 2 groups). This lack of significance in both items probably results from the high variance. In addition, visual memory was not affected by education level whereas almost all measures of the verbal memory were sensitive to EL. A putative explanation for this finding is that while using words, a highly educated individual can use education-dependent semantic strategies (eg, clustering words into semantic categories).

It is accepted that performance in neuropsychologic tests is influenced by intelligence and education,[22] but in previous reports this effect seems to be limited only for some tests (eg, MME),[12] and in those a reduced performance was seen only in very low educated (0 to 4 y) individuals.[23] Moreover, it was shown that although the use of cognitive screening tests that are associated with EL may influence the strength of the association between a low level of education and incident AD, these influences cannot completely explain this association.[24] Therefore, although we cannot completely rule out the possibility of some artifactual bias it seems plausible that the better scores achieved by our highly educated patients reflect a real effect of education on cognitive performance in PD.

Our findings can be explained in 2 ways. First, the "protective" possibility that assumes a slower rate of cognitive deterioration in highly educated individuals because education and mental activity can produce functional brain changes (like increased synaptic density or larger brain volume) that slows down cognitive decline associated with age or disease.[25] Second, the "reserve" possibility suggests that all patients regardless of their EL experience the same rate of cognitive deterioration as a result of the disease but in highly educated individuals the higher starting point prevent them from reaching a very low performance level.[26]

In an attempt to dissociate between the "protective" versus the "reserve" contribution of education, a longitudinal follow-up study should measure the cognitive functioning deterioration rate, of PD patients over time.

Our study has some limitations. Highly educated individuals were significantly younger than the other 2 groups. This may be due to historical reasons, that is, older patients had a lesser chance to attain formal education due to the second world war and in some cases the immigration to Israel. We overcame this limitation statistically by using age as a covariate. Highly educated patients also had a younger age of disease onset but this was not significant and in accordance with their younger age and, therefore, probably do not have an independent effect on the results. The male to female ratio was also different between the groups and although it was not statistically significant we cannot rule out some minor effect of sex.

The potential association we found between hallucinations and education is interesting, but warrants further investigation, because it was not shown in a former study.[27]

In conclusion, our results show an association between education and cognitive performance in patients with PD and suggest that education might modulate cognitive dysfunction in PD.

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