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The effect of age of disease onset on neuropsychological performance in Parkinson's disease

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SUMMARY One hundred and eight noninstitutionalised patients with Parkinson's disease were studied to find out whether the age of disease onset affects patients' cognitive, memory and psychomotor performance. "Early onset" patients (whose disease began before 60 years of age) showed a wide spectrum of impairments in neuropsychological performance compared with age-matched normal subjects. However, only one (2%) of these patients was demented according to DSM III criteria. Dementia was more frequent in patients with equivalent disease duration, but with late onset of disease (over 60 years); 13 of such patients (25%) were demented. The present study supports previous findings which show that dementia increases with advancing age in Parkinson's disease. It also suggests that cognitive changes are also found in patients with early onset of disease.

The great variation in the cognitive performance of individual patients and the differences in the severity of their extrapyramidal symptoms has given rise to the idea that idiopathic Parkinson's disease may encompass several subgroups. Some studies[1-3] indicate that dementia, greater motor disability and rapid symptom progression are linked with a later age of onset. Thus the existence of two groups has been suggested: a late onset "malignant" form and an early onset "benign" form of Parkinson's disease. The issue is controversial, however. Mjönes[4] observed the opposite to be the case, whereas Lesser *et al*[5] reported that individuals affected more severely are younger and have a shorter disease duration, and Hoehn and Yahr[6] found no connection between the age of onset and progression of the disease. These studies were not based on formal neuropsychological evaluation but on brief estimations of mental state, which are recognised as carrying a high false-positive rate. We have endeavoured to determine whether more comprehensive formal neuropsychological evaluation of cognitive functions could clarify the role of age at disease onset in modifying the cognitive performance and disease progression.

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Patients and methods

A total of 108 outpatients with Parkinson's disease between 32 and 86 years of age were studied, in whom the age of onset, whether below 60 years ("early onset") or over 60 years ("late onset"), could be estimated within an accuracy of at least 6 months. The distribution of age at onset is given in table 1. The clinical data on the patients are given in table 2 which shows that the duration of disease was equal in the two groups. These patients were selected by excluding those in whom the duration of disease exceeded 10 years or in whom the duration of disease obtained from the patient and his relatives, could not be verified from hospital or health care records. Furthermore, subjects with other diseases with possible adverse effects on cognitive performance were excluded from the study. Patients with controlled cardiac insufficiency and/or arterial hypertension were accepted. Of drugs with central nervous system effects, only treatment with small amounts of benzodiazepines and tricyclics, was allowed. Levodopa, with or without a decarboxylase inhibitor, anticholinergic drugs, amantadine and l-deprenyl (selegiline) were allowed. Since anticholinergic drugs have

Table 1 *The distribution of the patients' age at disease onset*

Age at onset (years)	*Number of patients*
20–29	1
30–39	12
40–49	19
50–59	17
60–69	45
70–79	12
80–	2

Table 2 *Clinical characteristics of Parkinsonian patients with the early onset and late onset of disease (mean ± SD)*

	Early onset	*Late onset*
Number of patients	49	59
Age (years)	49·0 ± 7·3	69·2 ± 5·8
Age of onset (years)	45·3 ± 8·1	65·8 ± 5·5
Disease duration (years)	3·7 ± 3·2	3·4 ± 2·4
Disease severity*		
Grade 1	1	3
Grade 2	23	13
Grade 3	21	35
Grade 4	4	8
Clinical disability†		
Tremor	1·1 ± 1·6	2·3 ± 2·1
Rigidity	6·1 ± 3·2	6·0 ± 3·8
Posture	1·0 ± 0·8	1·6 ± 0·8
Balance	0·4 ± 0·6	0·6 ± 0·8
Hypokinesia	12·3 ± 6·7	16·2 ± 9·3
Total score	19·5 ± 9·0	24·5 ± 12·0
Treatment		
Levodopa	7	13
Levodopa ± anticholinergics	7	7
Antichol treatment	6	10
Nontreated	29	29

*Hoehn and Yahr-scale.[6]
†Columbia University Parkinsonism Disability Rating Scale.[10]

been reported[7-9] to cause intellectual impairment, especially of memory functions, results were also analysed by excluding the patients receiving anticholinergic medication.

The patients' performance was compared with that of 55 healthy control subjects, mainly spouses of the patients but also healthy volunteers from a church bible group, matched for educational level and age. The same criteria for inclusion and exclusion were used as in patient selection. Of the total of 55 control subjects 20 were under 60 (47·4 ± 7·0, mean ± SD) and 35 over 60 (71·8 ± 7·7, mean ± SD) years of age.

Clinical neurological disability was evaluated using the Columbia University Parkinsonism Disability Rating Scale,[10] modified to include arm swing during walking. A score of 0 to 4 (0 = normal, 4 = maximal disability) was given separately for tremor and rigidity. A composite score for bradykinesia was derived by adding the scores for posture, gait, balance, finger dexterity, alternating movements, rising from a chair, facial expression and arm swing.

The neuropsychological studies consisted of tests measuring cognitive, memory and psychomotor functions. Cognitive functions were evaluated by using the subtests of similarities, picture completion and block design of the Wechsler[11] Adult Intelligence Scale (WAIS). The Wechsler Memory Scale I (WMS I) was used to evaluate memory functions using the subtests of digit span, logical memory, associative learning and visual memory.[12] Psychomotor functions were studied by measuring reaction time and movement time made with computer-controlled equipment. The movement and reaction time responses involved movement of the dominant hand over a distance of 32 cm. The subjects held their index finger on a button ("go" button) and received visual signals indicating the direction of the intended movement (left or right target) and when to move ("GO" signal). In the test of simple reaction time (SRT), the direction signal (either left or right) came on 2 to 4 s before the "GO" signal, whereas in the choice reaction time (CRT) test, they came on at the same time. Direction of successive movements and movement intervals varied at random. A mean value of 16 trials was scored for each subject in each reaction time experiment. In the results, the reaction times (in ms) refer to the latency between the "GO" signal and the beginning of the movement, and movement time (MT) refers to time taken (in ms) for a finger to move from the "GO" button to either of the two targets. Additional tests of psychomotor performance included the Purdue pegboard test, finger tapping speed (number of taps/10 s) and writing time (the time it took, in seconds, for all subjects to write the same sentence). Stroop's colour test which is particularly sensitive in subjects with frontal lesions was also used to evaluate psychomotor function (speech), the ability to follow a complex plan and inhibition of irrelevant elements.[13,14] Subtracting the time used to complete Stroop 2 from the time used for Stroop 3 (referred to as Stroop 3-2 in the results), was taken as an estimate of the ability to maintain a mental set. The Trail making test (part B) was performed in a standard manner, but was also qualitatively analysed using a modified scoring system reported to evaluate cognitive flexibility.[15] The performance of each subject was classified according to following the system: intact performance, sequence binding, retracing steps, illogical performance, giving up or ignoring one to two items.

Each patient's level of depression was evaluated with the Beck Depression Index.[16]

The evaluation of dementia was made on the basis of an interview with the patient and/or the relatives and estimated according to DSM III criteria.

Statistical analysis of the data utilising the chi-square test and Student's *t* test was performed using BMDP statistical computer software.[17] Student's *t* test was used after logarithmic transformation for those cases in which the results were not normally distributed. The results have also been analysed by using the z-scores.

Results

Patients with early onset Parkinsonism

The performance of patients with early disease onset (below 60 years) in the WAIS and WMS I subtests is presented in fig 1. Of the WAIS subtests, the performance of the patients with Parkinson's disease was worse than that of age-matched control subjects in block design ($p < 0.01$) and picture completion tests ($p < 0.05$). The patients were inferior to the normal subjects in three of four memory (WMS I) tests: logical memory ($p < 0.01$), associative learning ($p < 0.01$) and visual memory ($p < 0.05$). Tests evaluating cognitive flexibility (also necessitating some motor involvement) revealed inferior performance for the patients in the Stroop and Trail making tests (table 3). Qualitative analysis showed that the patients' performance was often incomplete (Pearson chi-square = 10·136, $p < 0.05$). Performance was incomplete in 43% of the patients but in 22% of the control subjects; a common error in the patient group was to ignore one or two items (letters or numbers). Not surprisingly, the patients' performance was also significantly worse than that of the control subjects in

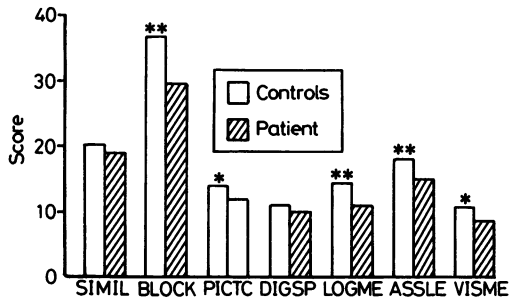

Fig 1 *Mean scores of cognitive (WAIS) and memory (WMS I) performance in 49 early onset patients with Parkinson's disease (dotted bars) and 20 age-matched control subjects (solid bars). The performance of the patients was not significantly different in WAIS-similarities (1), whereas in block design (2) and picture completion (3) they performed significantly ($p < 0.01$, $p < 0.05$) worse than controls. In memory tests the patients were inferior to the control subjects in logical memory (5, $p < 0.01$), associative learning (6, $p < 0.01$) and visual memory (7, $p < 0.05$), but not in digit span (4).*

all tests measuring psychomotor abilities (table 4): the reaction times and movement time were prolonged ($p < 0.05$), the simple tapping speed was diminished, the Purdue pegboard test was slower ($p < 0.001$), and writing took longer ($p < 0.001$) than for the control subjects.

The Beck Depression Index was 6·2 ± 4·8 (mean ± SD) for the patients and 2·4 ± 2·6 (mean ± SD) for the controls, the difference being significant ($p < 0.01$).

Patients with late onset Parkinsonism

The late onset patients differed ($p < 0.05$) from the age-matched control group only in block design subtest of WAIS (fig 2). The patients performed worse than the control subjects in the logical memory ($p < 0.01$) and visual memory ($p < 0.01$) subtests of WMS I (fig 2). Of the cognitive flexibility tests (table 2), the patients performed worse in the Stroop 2 ($p < 0.01$) and Trail-making tests ($p < 0.05$), but not in the Stroop 3 test. Likewise, the difference between Stroop 3 and Stroop 2 (Stroop 3-2), used to measure the ability to maintain a mental set, was not significant. Qualitative analysis of the Trail-making test revealed that only 16% of the patients could perform the task without error, whereas the respective figure for the controls was 58%. The difference in qualitative performance was highly significant (Pearson chi-square = 18·962, $p < 0.001$). Psychomotor performance of the patients with late onset (table 4) revealed longer simple ($p < 0.05$) and choice ($p < 0.01$) reaction times, a longer movement time ($p < 0.01$) and a longer writing time ($p < 0.001$) than in the control group.

The Beck Depression Index for the patients with late onset was also ($p < 0.001$) higher (6·3 ± 4·6, mean ± SD) than in the control subjects (2·4 ± 2·2, mean ± SD).

Table 3 *Performance of Parkinsonian patients and control subjects in tests evaluating psychomotor functions and cognitive flexibility*

	Early onset patients (N = 49)	*Young control subjects (N = 20)*	*Significance*
Stroop 2	68·6 ± 22·0	48·3 ± 12·7	$p < 0.001$
Stroop 3	146·6 ± 73·3	89·4 ± 22·1	$p < 0.01$
Stroop 3-2	78·0 ± 59·3	41·1 ± 20·2	$p < 0.05$
Trail making	158·0 ± 86·6	96·2 ± 43·8	$p < 0.01$
	Late onset patients (N = 59)	*Elderly control subjects (N = 35)*	*Significance*
Stroop 2	142·0 ± 124·6	84·5 ± 57·0	$p < 0.01$
Stroop 3	258·8 ± 147·5	217·0 ± 137·7	$p > 0.05$
Stroop 3-2	115·9 ± 105·0	136·6 ± 116·4	$p > 0.05$
Trail making	294·0 ± 138·8	232·3 ± 157·7	$p < 0.05$

Table 4 *Psychomotor performance in 49 early onset Parkinsonian patients compared with 20 age-matched control subjects*

	Parkinsonian patients	*Age-matched controls*	*Significance*
SRT (ms)	401·5 ± 132·6	324·3 ± 68·7	$p < 0.05$
CRT (ms)	430·7 ± 102·2	371·6 ± 59·3	$p < 0.05$
MT (ms)	494·4 ± 424·0	277·4 ± 88·5	$p < 0.05$
Tapping speed (n of taps/10 s):			
Dominant hand	37·8 ± 9·4	50·4 ± 8·0	$p < 0.001$
Nondominant hand	33·4 ± 10·6	46·2 ± 6·5	$p < 0.001$
Purdue pegboard (n of pins/30 s):			
Dominant hand	11·7 ± 2·5	15·9 ± 1·7	$p < 0.001$
Nondominant hand	11·1 ± 2·3	14·9 ± 1·6	$p < 0.001$
Bimanual performance	8·1 ± 2·0	13·5 ± 1·9	$p < 0.001$
Writing time (s)	14·2 ± 5·7	8·3 ± 3·1	$p < 0.001$

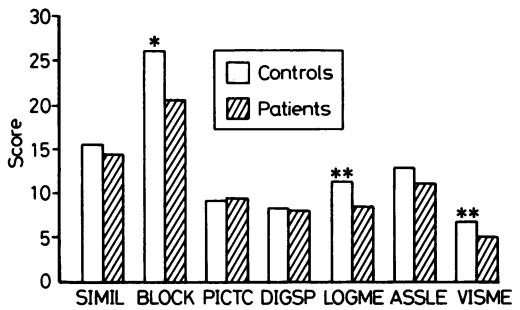

Fig 2 *Mean scores of cognitive (WAIS) and memory (WMS I) performance in 59 late onset patients with Parkinson's disease (dotted bars) and 35 age-matched control subjects (solid bars). In WAIS subtests the patients performed significantly ($p < 0.05$) worse only in block design (2) whereas in similarities (1) and picture completion (3) the difference was not significant. In memory tests the patients were inferior to the control subjects in logical memory (5, $p < 0.01$) and visual memory (7, $p < 0.01$) but not in associative learning (6) and digit span (4).*

Comparison of the early and late onset Parkinsonism

The patients with late onset performed worse than those with early onset in all cognitive and memory functions ($p < 0.01$–0.001). They were also inferior in tests of cognitive flexibility and psychomotor capacity. The degree of depression was identical in the two groups. The inter-individual variation was more marked in the late onset group. Figure 3 illustrates the degree of variability in memory functions of the two groups.

To take into account possible age-related cognitive changes in the control subjects, the results were transformed into z-scores. The age-matched control subjects for both patient groups were used as respective standard populations to represent the zero level. This data on WAIS and WMS I is shown in fig 4 and the results of the psychomotor measurements are given in fig 5. The figures confirmed the results of previous comparisons showing that the early onset patients differentiated even more from their age-matched control group than the late onset patients from their controls. Statistically significant differences between the early and late onset patients were observed in picture completion ($p < 0.01$), associative learning ($p < 0.01$), movement time ($p < 0.05$), Stroop 3 ($p < 0.001$), Stroop 3-2 ($p < 0.001$), Trail making ($p < 0.01$), Purdue pegboard performance with both the dominant hand ($p < 0.001$) and nondominant hand ($p < 0.05$) as well as bimanually ($p < 0.001$).

To study whether the differences between the early onset and late onset group would be even clearer at the most extreme age groups, patients with disease onset under 45 years of age were compared with those with disease onset over 70 years of age. This was not the case. The profile of performance and its statistical significances were practically identical to that illustrated in figs 4 and 5.

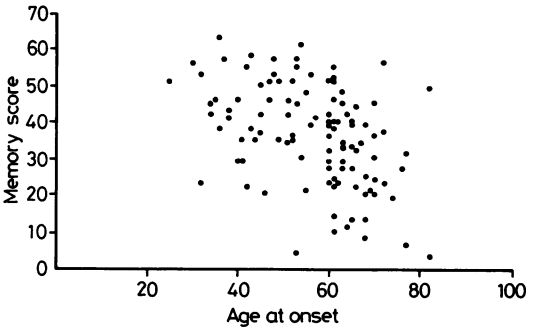

Fig 3 *A scatter plot of memory functions (sum score of WMS I subtests) according to age at disease onset in the total patient material studied.*

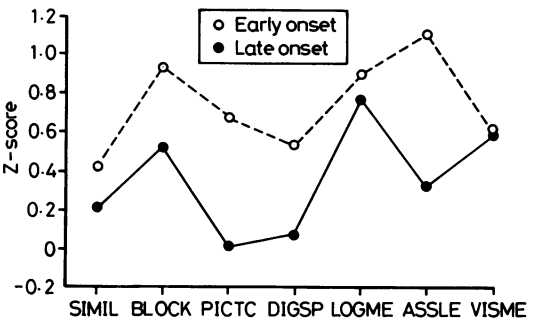

Fig 4 *The z-scores of WAIS and WMS I subtests in the early onset and late onset patient groups. The differences in the z-scores of these groups were significant in picture completion ($p < 0.01$) and associative learning ($p < 0.01$), other remained statistically nonsignificant.*

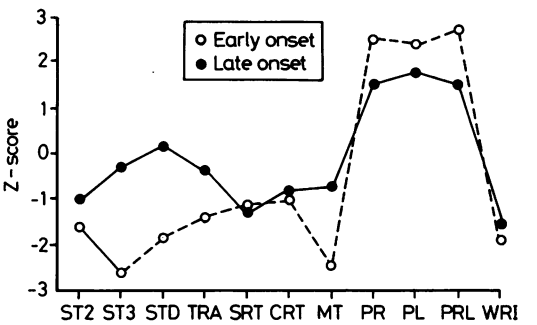

Fig 5 *The z-scores of psychomotor and cognitive flexibility tests in the early onset and late onset patient groups. The differences in the z-scores were significant in Stroop 3 ($p < 0.001$), Stroop 3-2 ($p < 0.001$), Trail making ($p < 0.01$), movement time ($p < 0.05$), Purdue pegboard of the dominant (0.001) and nondominant hand ($p < 0.05$) as well as in bimanual performance ($p < 0.001$).*

Table 5 *Psychomotor performance in 59 late onset Parkinsonian patients compared with 35 age-matched control subjects*

	Parkinsonian patients	*Age-matched controls*	*Significance*
SRT (ms)	530·3 ± 299·7	396·9 ± 107·8	$p < 0.05$
CRT (ms)	586·7 ± 215·4	480·9 ± 127·2	$p < 0.01$
MT (ms)	626·1 ± 277·6	456·9 ± 229·3	$p < 0.01$
Tapping speed (n of taps/10 s):			
Dominant hand	35·4 ± 9·6	39·3 ± 7·7	$p < 0.05$
Nondominant hand	32·7 ± 8·9	36·3 ± 7·7	$p < 0.05$
Purdue pegboard (n of pins/30 s):			
Dominant hand	8·6 ± 3·4	12·7 ± 2·8	$p < 0.001$
Nondominant hand	7·9 ± 3·2	12·1 ± 2·4	$p < 0.001$
Bimanual performance	5·9 ± 2·8	9·6 ± 2·5	$p < 0.001$
Writing time (s)	24·8 ± 18·7	14·1 ± 6·9	$p < 0.001$

Table 6 *Clinical data on the extreme groups according to the age at onset*

	Onset before 45 years of age	*Onset after 70 years of age*
Number of patients	12	14
Age at onset	37·7 ± 5·3	74·0 ± 4·3
Age at examination	41·7 ± 4·1	76·8 ± 4·8
Disease duration	4·1 ± 3·1	2·9 ± 1·9
Tremor	0·8 ± 1·3	1·4 ± 2·0
Rigidity	6·1 ± 2·4	4·6 ± 3·1
Hypokinesia	11·7 ± 5·7	16·3 ± 8·1
Total scores*	18·5 ± 8·0	22·3 ± 10·0

*Columbia University Parkinsonism Disability Rating Scale[10].

According to DSM III criteria, 13 (25%) of the late onset patients were demented; the corresponding figure was one (2%) in the early onset group in spite of the similar duration of the disease.

A statistical analysis was also carried out after excluding the patients treated with anticholinergic drugs. At the time of the examination anticholinergic drugs were used by 13 patients in the early onset group and 17 patients in the late onset group. The exclusion of these subjects did not essentially change the results.

Discussion

Several clinical studies have reported that the frequency of dementia in patients with Parkinson's disease increases with advancing age,[2 18 19] mental capacity being preserved in a younger patient population.[20] Some authors[1 3] have even postulated that there are two clinically and possibly pathologically distinct forms of idiopathic Parkinson's disease: younger patients have a relatively pure motor disorder with a longer and more benign course, and better response to levodopa treatment, whereas in older patients the symptom complex includes a motor disorder followed by cognitive decline with a more fulminant course and poor response to levodopa.

The present neuropsychological study indicates that the previous clinical impression, albeit valid in many respects, is not the whole truth. Our study also shows that the performance of the patients with late onset disease is significantly inferior to that of the patients with early onset. On the other hand, the patients with early onset disease also performed less well than their age-matched control subjects in a number of individual tests evaluating cognitive and memory functions. The memory deficit was evident in all tests requiring mental processing of material but not in a simple test of immediate retrieval (digit span). The same kind of memory pattern, distinguishing between effort-demanding and automatic memory processes, has previously been reported at an early stage of the disease in untreated patients.[21 22] Evaluation of cognitive functions showed that the patients with early disease onset have impairments in cognitive flexibility and in the ability to maintain a mental set, as has previously been reported in untreated patients at an early stage of the disease[22 23] and in patients treated with levodopa.[24]

Contrary to previous reports[1 20] the early onset patients were thus impaired on several measures of cognitive and psychomotor functions. This difference in results was probably caused by the methods used to evaluate the patients' mental functions. We used formal neuropsychological methods, whereas the studies referred to were based on a brief mental status evaluation. These simple tests may well be suitable for revealing more profound impairments in mental ability, yet not sensitive enough for the discrimination of milder cognitive changes.

The degree of cognitive impairment and its variability in older patients deserves a separate comment. The various cognitive and memory functions of our late onset patients were significantly more impaired than those of early onset patients. In this respect, our results are consistent with the findings of Jellinger and Riederer[25] that brain atrophy in Parkinson's disease is more closely associated with aging than with the duration of the disease. The differences between the early onset patients and age-matched normal controls in some subtests of memory functions (learning) and cognitive flexibility were not so clear in the late onset group in comparison with the control subjects. The reason for this is not clear, but could be, at least partially, that impairments in these functions are

significantly age-related. We calculated that memory functions were reduced by about 20–33% and cognitive flexibility by as much as 20–70% between approximately 45 and 75 years of age in the control population. However, this decline ascribed to aging may be an overestimation, since cross-sectional or cohort studies may show greater changes than follow-up studies.[26] Individual differences also became more marked with advancing age in both the controls and patients. These large intragroup deviations (for example, table 3 and fig 3) are likely to be one reason for the decreased statistical significance of the differences between the patients with late onset and their controls.

According to DSM III criteria, 13 (25%) of the late onset patients were demented; the corresponding figure was one (2%) in the early onset group in spite of the similar duration of the disease. This one demented patient in the early onset group was, in spite of evident Parkinsonian symptomatology, exceptional in having a very rapid progression of symptoms and a poor response to levodopa. In the older control group, there were three subjects (8%) who fulfilled the same criteria. This may be an underestimate of the true incidence, since some of our control subjects, who actively take part in church activities, may represent a mentally better-preserved group.

We believe that the present results support previous findings in that the frequency of dementia in patients with Parkinson's disease increases with advancing age.[2 19] Our results also show, however, that the decline is extremely variable. One explanation for such variance in mental capacity of patients with late onset Parkinson's disease was provided by Quinn *et al*[27] who estimated that 5% of patients over 65 years with clinical Parkinson's disease would, by chance, have Alzheimer disease, and that an additional 10% or so might have combined pathology sufficient to cause dementia. Accordingly, a population with late onset Parkinson's disease may, as a consequence of independent age-related changes, have an additional risk of dementia.[28]

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