Extrapyramidalism in Alzheimer's disease: prevalence, psychiatric, and neuropsychological correlates

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Abstract

The prevalence and clinical correlates of extrapyramidal signs in a consecutive series of 78 patients with Alzheimer's disease attending a neurology clinic, and 20 age comparable normal controls, were examined. Based on the unified Parkinson's disease rating scale (UPDRS) findings, 18 patients (23%) met criteria for parkinsonism, 44 (56%) had isolated extrapyramidal signs, and 16 (21%) had no extrapyramidal signs. Whereas the control group showed a similar prevalence of isolated extrapyramidal signs (57%), none of them showed parkinsonism. No significant differences were found for age, sex, duration of illness, and severity of dementia among the three Alzheimer's disease groups. Patients with Alzheimer's disease-parkinsonism, however, showed a significantly higher frequency of major depression and dysthymia and significantly higher Hamilton depression scores than patients with isolated or no extrapyramidal signs. Patients with Alzheimer's disease-parkinsonism also showed significantly more deficits on frontal lobe related tasks such as the Wisconsin card sorting test, trail making test, and verbal fluency, as well as on tests of constructional praxis and abstract reasoning than patients with Alzheimer's disease but no extrapyramidal signs. In conclusion, the study showed a specific association between Alzheimer's disease and parkinsonism, as well as significant relations between parkinsonism, deficits in executive functions, and depression among patients with Alzheimer's disease.

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Extrapyramidal signs are well known features of Alzheimer's disease. Molsa *et al*¹ examined 143 patients with probable Alzheimer's disease for the presence of extrapyramidal signs and found that only 8% of them had no signs. A limitation of this study, however, was that a group of normal controls was not assessed, and whether the prevalence of extrapyramidal signs in Alzheimer's disease was comparable with that found in non-demented people of a similar age could not be determined. In a recent community based study, Funkenstein *et al*² showed that diminished spontaneous

movements of the limbs or face, reduced arm swing in walking, and gait abnormalities were associated with a substantially increased probability of having clinically diagnosed Alzheimer's disease. Whether this increased frequency of extrapyramidal signs was part of a parkinsonian syndrome or only consisted of isolated extrapyramidal signs was not established. The delineation of a subgroup of patients with Alzheimer's disease and extrapyramidal signs has important clinical implications, as this group was reported to have a faster cognitive decline and a higher mortality.³

The mechanism of extrapyramidal signs in Alzheimer's disease is poorly understood. Whereas some studies have shown neuropathological similarities between Parkinson's disease and Alzheimer's disease with extrapyramidal signs,^{4,5} others showed neither dysfunction of the nigrostriatal dopaminergic terminals⁶ nor response to levodopa treatment.⁷ The apomorphine test is regularly used for the diagnosis of Parkinson's disease, with a sensitivity of 70-90%.⁸ To the best of our knowledge, this test has not been assessed in patients with Alzheimer's disease and extrapyramidal signs. Whether this group of patients shows either a positive or a negative response to apomorphine may shed more light on the mechanism of extrapyramidal signs in Alzheimer's disease.

Depression is also a frequent finding among patients with Alzheimer's disease, and has been reported in 30-40% of consecutive patients.⁹ A similar prevalence of depression has been documented in patients with Parkinson's disease,¹⁰ but the possibility that Alzheimer's disease with extrapyramidal signs may be significantly associated with depression has rarely been examined. Bakchine *et al*¹¹ have recently reported that depressed patients with Alzheimer's disease had significantly higher akinesia scores than patients with Alzheimer's disease but without depression. This study had limitations, as the diagnosis of depression was not based on clinical criteria, a structured psychiatric interview was not carried out, and patients with Alzheimer's disease taking neuroleptics were not excluded.

Although several studies showed that patients with Parkinson's disease, even in the absence of dementia, have deficits in specific cognitive functions, such as planning, set shifting, and abstract reasoning,¹² neuropsychological differences between patients with Alzheimer's disease and with or without extrapyramidal signs have rarely been

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examined. Girling and Berrios¹³ assessed a group of 146 patients with Alzheimer's disease and found a significant association between extrapyramidal signs and deficits in frontal lobe related functions, such as verbal fluency and perseverations. Patients taking neuroleptics or other drugs that could potentially induce extrapyramidal signs were not excluded, however, and a comprehensive neuropsychological battery was not used.

We examined a consecutive series of patients with Alzheimer's disease for the presence of extrapyramidal signs. Our main goals were to determine the prevalence of extrapyramidal signs in Alzheimer's disease, to assess the response of patients with Alzheimer's disease and extrapyramidal signs to apomorphine, and to examine the associations between Alzheimer's disease, extrapyramidal signs, the pattern of cognitive deficits, and the prevalence of depression.

Patients and methods

PATIENTS

A consecutive series of 103 patients who attended the neurology clinic of our Institute because of progressive cognitive decline were screened for inclusion in this study. The inclusion criteria were (a) NINCDS-ADRDA¹⁴ criteria for probable Alzheimer's disease; (b) no history of closed head injuries with loss of consciousness, strokes or other neurological disorders with CNS involvement; (c) normal results on laboratory tests; (d) no focal lesions on CT; (e) a Hachinski ischaemic score ≤ 4 ¹⁵; and (f) no past or present intake of drugs that could produce extrapyramidal signs (neuroleptics, calcium channel blockers, chronic use of antiemetics). Seventy eight patients met the criteria and were included. We also examined 20 age comparable healthy subjects with no history of neurological or psychiatric disorders and no past or present intake of drugs that could produce extrapyramidal signs.

NEUROLOGICAL EXAMINATION

After informed consent patients and controls were assessed with the unified Parkinson's disease rating scale (UPDRS).¹⁶ This scale has three sections: (a) activities of daily living; (b) motor examination; and (c) complications of antiparkinsonian treatment. Items scores range from 0 to 4, and higher scores indicate more severe impairments. Based on the motor section scores of the UPDRS, patients were divided into the following groups: (a) Alzheimer's disease-Parkinsonism: patients included in this group had rigidity, bradykinesia, and resting tremor, rigidity plus bradykinesia only, or resting tremor only. Bradykinesia was defined as a score >1 on the finger tapping, rapid hand movements, and alternating movements of the hands sections of the UPDRS. Rigidity was defined as a score >1 in the UPDRS (only cogwheel rigidity was considered); (b) Alzheimer's disease-extrapyramidal signs: patients included in this group had extrapyramidal signs other

than bradykinesia, rigidity, or resting tremor (flexed posture, gait disorders, masked face); and (c) Alzheimer's disease-no extrapyramidal signs: patients included in this group scored 0 on every item on the motor section of the UPDRS.

APOMORPHINE TEST

Patients who met the criteria for Alzheimer's disease-parkinsonism received 60 mg of domperidone daily for at least 48 hours before the test.⁸ A basal examination was carried out in the fasting state at 0900 and included the Webster scale (a scale that measures motor disabilities),¹⁷ the number of taps produced when patients were asked to tap alternatively on two keys situated 20 cm apart with the more affected hand in 30 seconds, and the time to rise from an armless chair, walk 6 metres, come back, and sit down. We decided to use the Webster scale instead of the UPDRS as the first has usually been used to assess motor changes after apomorphine injection. After the basal assessment, 3 mg of apomorphine were injected subcutaneously, and the neurological assessment was repeated every 15 minutes for one hour. Criteria for a positive response were an increase in tapping $>15\%$ and of walking speed $>20\%$ and a decrease in the Webster score ≥ 3 points.¹⁸

PSYCHIATRIC EXAMINATION

The psychiatric evaluation included the following assessments:

*Structured clinical interview for DSM-III (SCID)*¹⁹

The SCID is a semistructured diagnostic interview for making the major axis I DSM-III-R diagnoses. The SCID was given by a psychiatrist blind to the remaining clinical data, and the interview was carried out with the patient and at least one first degree relative. Based on the SCID responses, DSM-III-R diagnoses of major depression and dysthymia were made.

*Hamilton depression scale (HAM-D)*²⁰

The HAM-D is a 17 item interviewer rated scale that measures psychological and autonomic symptoms of depression.

NEUROPSYCHOLOGICAL EXAMINATION

Patients received a comprehensive neuropsychological evaluation that consisted of the following tasks:

*Mini mental state exam (MMSE)*²¹

The MMSE is an 11 item examination that has been found to be reliable and valid in assessing a limited range of cognitive functions in patients with dementia.

*Buschke selective reminding test*²²

This test measures verbal learning and memory during a multiple trial list learning task. The patient listens to a list of words, and has to recall as many words as possible. Each subsequent learning trial involves the selective presentation of only those words that were not

recalled on the immediately preceding trial. The outcome measures are the long term retrieval and the delayed recall scores.

*Benton visual retention test*²³

This test assesses visual perception and non-verbal memory. Patients are exposed to geometric designs for 10 seconds and are immediately presented with a card containing the correct design among three different foils. The patient has to select the correct one.

*Apraxia subtest of the western aphasia battery*²⁴

This test assesses the presence of ideomotor apraxia.

*Block design (WAIS)*²⁵

This test examines the presence of constructional apraxia. Patients are presented with red and white blocks and are asked to construct replicas of printed designs. Time to completion was not considered in the final score.

*Digit span*²⁵

This test examines auditory attention and includes two parts. Both consist of seven pairs of random number sequences that the examiner presents at the rate of one per second. In the first part (digits forward), the patient is asked to repeat a string of numbers (from 2 to 8) exactly as it is given, and in the second (digits backwards) the patient is asked to repeat a string of numbers (from 2 to 8) in reverse order.

*Wisconsin card sorting test (WCST)*²⁶

This test measures the ability to develop new concepts and shift sets, and also requires the subjects to suppress a previously correct response and produce a new one. Assessment of the overall proficiency of the test was judged by the number of categories achieved (maximum 6). Because of the rather large number of cognitive tests assessed, we decided to use number of categories as the single endpoint for this task.

*Trail making test*²⁷

This test examines visual, conceptual, and visuomotor tracking. The patient is instructed to draw lines to connect consecutively numbered circles on a paper (part A), and then connect the same number of consecutively numbered and lettered circles on another paper by alternating between the two

sequences (part B). The patient is urged to connect the circles as quickly as possible. To control for graphomotor speed and visual scanning the final score was the time to complete part A minus the time to complete part B.

*Controlled oral word association test*²⁸

This test examines access to semantic information with time constraint. Patients were instructed to name as many words beginning with the letter F as they could in one minute. People's names and proper nouns were not permitted. The letters A and S were then presented successively, one minute being allowed for each letter. The score was the number of words produced in one minute.

*Boston naming test*²⁹

This test measures the ability to name pictured objects. Line drawings of high and low frequency objects are presented one at a time on cards, which the patient has to name.

*Token test*³⁰

This test measures verbal comprehension of commands of increasing complexity.

*Raven's progressive matrices*³¹

This test measures visuospatial reasoning. Patients are presented with a pattern problem with one part removed and several pictured inserts, one of which contains the correct pattern. The patient has to select the missing piece to complete the pattern.

The whole testing session lasted between 60 and 120 minutes. Because some of the patients showed fatigue during the assessment, they were allowed to split the cognitive assessment into two or three sessions.

STATISTICAL ANALYSIS

Statistical analysis was carried out on means and SDs by analysis of covariance (ANCOVA), and post hoc *t* tests. Regressions were calculated with a stepwise forward regression analysis (*F* to enter = 1.0), and frequency distributions were calculated with contingency tables, Fisher's exact tests, and χ^2 tests with a Yates' correction for cell sizes <5. All *p* values are two tailed.

Results

DEMOGRAPHIC FINDINGS (TABLE 1)

No significant between group differences were found for age, sex, education, duration of illness, and family and personal history of psychiatric disorders. The mean (SD) age of the control group was 70.9 (8.1). There were 13 women and seven men.

NEUROLOGICAL FINDINGS (TABLE 2)

Sixteen of the 78 patients with Alzheimer's disease (21%) had no extrapyramidal signs, 44 patients (56%) showed isolated extrapyramidal signs, and 18 patients (23%) had parkinsonism. None of the 20 normal controls had parkinsonism, but 12 of them (57%) showed isolated extrapyramidal signs ($\chi^2 =$

Table 1 Demographic and psychiatric findings

	Alzheimer's disease- parkinsonism	Alzheimer's disease- extrapyramidalism	Alzheimer's disease-no extrapyramidalism
Patients (n)	18	44	16
Age (y)	74.9 (6.6)	72.4 (7.6)	71.8 (7.2)
Sex (M/F)	4/14	11/33	4/12
Education (y)	9.4 (5.3)	10 (5.3)	10.5 (4.1)
Duration of illness (y)	4.1 (2.8)	4.2 (2.6)	4.7 (2.6)
HAM-D scale**	15.3 (9.8)	10.6 (6.5)	5.8 (4.9)
Major depression***	6 (34%)	9 (20.5%)	0
Dysthymia	8 (44%)	15 (34.5%)	4 (25%)
No depression	4 (22%)	20 (45%)	12 (75%)

Values are mean (SD) or No (%).

p* < 0.01; *p* < 0.001.

Table 2 Neurological findings

	Alzheimer's disease- parkinsonism	Alzheimer's disease-isolated extrapyramidalism	Normal controls
Resting tremor	8 (44)	0	0
Masked face	12 (66)	24 (54)	5 (25)
Abnormal speech	8 (44)	5 (11)	0
Finger tapping	14 (77)	13 (29)	2 (10)
Action tremor	8 (44)	8 (18)	1 (5)
Rigidity	15 (83)	17 (38)	8 (40)
Hand movements	17 (94)	9 (20)	1 (5)
Alternating movements	17 (94)	12 (27)	1 (5)
Leg agility	15 (83)	12 (27)	1 (5)
Rising from a chair	13 (68)	19 (43)	1 (5)
Abnormal posture	13 (68)	24 (54)	5 (25)
Abnormal gait	9 (50)	18 (40)	2 (10)
Postural instability	7 (38)	18 (40)	1 (5)
Body bradykinesia	12 (66)	25 (56)	1 (5)
UPDRS (total motor score)	14.1 (7.7)	4.5 (4.8)	2.8 (1.8)

Values are No (%) except for UPDRS which is mean (SD).

Table 3 Mean (SD) neuropsychological findings

	Alzheimer's disease- parkinsonism	Alzheimer's disease-isolated extrapyramidalism	Alzheimer's disease-no extrapyramidalism
Buschke LTR	16.5 (9.1)	19.4 (18.7)	19.7 (24.2)
Buschke delayed	2.4 (1.7)	2.2 (3.1)	1.4 (2.7)
Apraxia (WAB)	56.2 (4.1)	56 (7.8)	58.0 (3.8)
Digits backward (WAIS)*	3.0 (0.9)	3.0 (1.2)	4.0 (1.0)
Wisconsin card sorting*	1.1 (1.5)	1.8 (2.1)	3.2 (1.9)
Trail making test (A-B)*	-339 (150)	-254 (141)	-181 (142)
Block design*	2.2 (2.2)	2.3 (2.2)	4.9 (1.9)
Controlled oral word association	23.0 (6.4)	28.2 (10.5)	30.6 (10.8)
Boston naming test	12.0 (4.0)	12.5 (5.8)	14.0 (4.2)
Token test	17.3 (6.8)	15.7 (8.0)	19.4 (7.9)
Raven's progressive matrices*	22.8 (27.7)	30.4 (29.8)	55.7 (32.7)
Mini mental state exam	18.3 (5.3)	18.5 (6.6)	20.5 (6.1)
Benton visual retention test	4.5 (2.0)	4.1 (2.3)	5.3 (2.8)

* $p < 0.05$.

10.4, $df = 2$, $p < 0.005$). This difference was accounted for by the significantly higher prevalence of parkinsonism in patients with Alzheimer's disease compared with normal controls (χ^2 Yates = 5.41 $df = 1$, $p < 0.02$). On the other hand there were no significant between group differences in the frequency of isolated extrapyramidal signs ($\chi^2 = 1.27$, $df = 1$, $p = 0.25$).

Only eight patients (10%) showed resting tremor, which was bilateral, mild, and variable in five patients, and persistent in the other three. Bradykinesia or rigidity were always present in the Alzheimer's disease-parkinsonism group. The remaining motor signs were also significantly more frequent in the Alzheimer's disease-parkinsonism group than in the Alzheimer's disease-isolated extrapyramidal signs group (table 2).

APOMORPHINE TEST

Eleven of the 18 Alzheimer's disease-parkinsonism group patients underwent the apomorphine test (five patients refused and two patients could not be localised). The mean (SD) Webster scores, tapping scores, and walking speed at basal examination were 9.9 (3.8), 37.6 (12.1), and 17.4 (3.3), respectively. There were no clinical improvements after the apomorphine injection. Thirty minutes after apomorphine injection, mean (SD) Webster scores, tapping scores, and walking

speed were 9.7 (4), 36.3 (10.5), and 17.4 (3.3) respectively, and none of these differences were significant ($t = 1.4$, 1.4 , and 1.0 respectively; $p > 0.10$). Side effects were present in all the 11 patients, and consisted of mild and transient nausea, yawning, and somnolence, which started five to 10 minutes after the injection and lasted for 15 to 30 minutes.

PSYCHIATRIC FINDINGS

A one way analysis of variance (ANOVA) for HAM-D scores showed significant between group differences ($F(2,75) = 7.56$, $p < 0.001$). On individual comparisons, patients with Alzheimer's disease-parkinsonism had significantly higher HAM-D scores than patients with either isolated extrapyramidal signs ($p < 0.02$), or no extrapyramidal signs ($p < 0.0002$), whereas patients with isolated extrapyramidal signs showed significantly higher HAM-D scores than patients with Alzheimer's disease and no extrapyramidal signs ($p < 0.02$). A hypothesis of equal frequency of dysthymia and major depression based on the presence of parkinsonism, isolated extrapyramidal signs, or no extrapyramidal signs was statistically rejected ($\chi^2 = 13$, $df = 4$, $p = 0.007$). On individual comparisons, patients with Alzheimer's disease-parkinsonism showed a significantly higher frequency of major depression and dysthymia than the Alzheimer's disease-no extrapyramidal signs group (Fisher's exact test $p = 0.002$ and $p = 0.03$ respectively).

To determine those factors that most significantly correlated with parkinsonism in Alzheimer's disease, we carried out a stepwise regression analysis in which the motor UPDRS score was the dependent variable and age, duration of illness, age at onset of dementia, MMSE, and HAM-D scores were the independent variables. The regression analysis was significant ($R^2 = 0.26$, $F(4,73) = 6.5$, $p = 0.0004$), and the variables that accounted for most of the variance were the HAM-D scores ($R^2 = 0.03$, $p < 0.0001$), and age ($R^2 = 0.07$, $p < 0.0001$).

NEUROPSYCHOLOGICAL FINDINGS

A multiple analysis of covariance (MANCOVA) for the neuropsychological evaluation (group: Alzheimer's disease-parkinsonism, Alzheimer's disease-isolated extrapyramidal signs, Alzheimer's disease-no extrapyramidal signs; covariate: Hamilton depression scale scores; independent variables: neuropsychological tasks) showed a significant main effect (Wilks' λ (28,122) = 0.55, $p < 0.05$). Independent MANCOVAs for each neuropsychological test showed significant between group differences on the following: Wisconsin card sorting test ($F(2,74) = 6.59$, $p < 0.01$), controlled oral word association test ($F(2,74) = 3.88$, $p < 0.05$), Raven's progressive matrices ($F(2,74) = 6.40$, $p < 0.01$); digits backward ($F(2,74) = 4.46$, $p < 0.05$); block design ($F(2,74) = 8.15$, $p < 0.001$), and trail making test ($F(2,74) = 6.92$, $p = 0.01$). No significant between group differences were found on the Buschke selective reminding test, Benton

visual retention test, token test, Boston naming test, digits forward, and ideomotor apraxia. On individual comparisons, the Alzheimer's disease-parkinsonism group showed significantly lower scores than the Alzheimer's disease-normal group on the Wisconsin card sorting test ($F(1,31) = 18.2$, $p < 0.001$), trail making test ($F(1,31) = 19.3$, $p < 0.001$), controlled oral word association test ($F(1,31) = 11.2$, $p < 0.001$), Raven's progressive matrices ($F(1,31) = 8.13$, $p < 0.01$), digits backward ($F(1,31) = 11.5$, $p = 0.001$), and block design ($F(1,31) = 8.86$, $p < 0.01$). The Alzheimer's disease-isolated extrapyramidal signs group showed significantly lower scores than the Alzheimer's disease-normal group on the Raven's progressive matrices ($F(1,57) = 8.13$, $p < 0.01$), Benton visual retention test ($F(1,57) = 4.45$, $p < 0.05$), Wisconsin card sorting test ($F(1,57) = 7.55$, $p < 0.01$), trail making test ($F(1,57) = 8.13$, $p = 0.01$), and block design ($F(1,57) = 17.1$, $p < 0.001$). Finally, the Alzheimer's disease-parkinsonism group showed significantly lower scores than the Alzheimer's disease-isolated extrapyramidal signs group on the trail making test ($F(1,59) = 5.01$, $p < 0.05$) and the controlled oral word association test ($F(1,59) = 3.70$, $p = 0.05$).

As there was a difference (although not significant) in MMSE scores between the Alzheimer's disease-parkinsonism group and the Alzheimer's disease-no extrapyramidal signs group, we compared the 16 patients in the Alzheimer's disease-no extrapyramidal signs group with the 16 patients in the Alzheimer's disease-parkinsonism group, excluding the two patients from the Alzheimer's disease-parkinsonism group with the lowest MMSE scores. Although mean MMSE scores were similar for both groups (Alzheimer's disease-parkinsonism (mean (SD)) = 20.0(5.9), Alzheimer's disease-no extrapyramidal signs = 20.5 (6.1), an ANCOVA for the neuropsychological tasks still showed significant between group differences on the Wisconsin card sorting test ($F(1,26) = 4.68$, $p < 0.05$), the trail making test ($F(1,26) = 6.38$, $p < 0.01$), and the Raven's progressive matrices ($F(1,26) = 5.04$, $p < 0.05$).

To further examine the association between extrapyramidal signs and deficits in specific cognitive domains, we carried out a forward stepwise regression analysis including the UPDRS scores as the dependent variable and HAM-D, MMSE, and the neuropsychological tasks as independent variables. There was an overall significant correlation between the total score on the motor section of the UPDRS and the independent variables ($R^2 = 0.38$, $F(6,71) = 7.21$, $p < 0.001$). The variables that accounted for most of the variance were the Raven's progressive matrices ($R^2 = 0.16$, $p < 0.05$), the Wisconsin card sorting test ($R^2 = 0.08$, $p < 0.05$), and HAM-D scores ($R^2 = 0.08$, $p < 0.01$). Resting tremor only showed a marginal correlation with the neuropsychological scores ($R^2 = 0.13$, $F(4,73) = 2.60$, $p < 0.05$), and none of the cognitive

tasks correlated significantly with tremor scores. Rigidity showed a significant overall correlation with the cognitive tasks ($R^2 = 0.28$, $F(5,72) = 5.30$, $p < 0.001$), and the variables that accounted for most of the variance were the Raven's progressive matrices ($R^2 = 0.09$, $p < 0.01$), the block design ($R^2 = 0.12$, $p < 0.001$), and the trail making test ($R^2 = 0.04$, $p = 0.05$). Finally, bradykinesia also showed a significant correlation with the neuropsychological tasks ($R^2 = 0.30$, $F(5,73) = 5.65$, $p < 0.0002$), and the variables that accounted for most of the variance were the Raven's progressive matrices ($R^2 = 0.10$, $p = 0.005$), the Benton visual retention test ($R^2 = 0.07$, $p = 0.02$), the Wisconsin card sorting test ($R^2 = 0.05$, $p < 0.03$), and ideomotor apraxia ($R^2 = 0.04$, $p < 0.05$).

Discussion

This study examined the prevalence, psychiatric and cognitive correlates, and response to apomorphine of extrapyramidal signs in patients with Alzheimer's disease, and showed four main findings. Firstly, 23% of the patients showed parkinsonism, 56% showed isolated extrapyramidal signs, and only 21% had no extrapyramidal signs. Whereas the frequency of parkinsonism was significantly higher than in age comparable normal controls, the prevalence of isolated extrapyramidal signs was not significantly different. Secondly, parkinsonism in Alzheimer's disease failed to improve after the apomorphine test. Thirdly, patients with Alzheimer's disease-parkinsonism had significantly more severe deficits on neuropsychological tasks assessing abstract reasoning, set shifting abilities, and executive functions than patients with Alzheimer's disease but no extrapyramidal signs, whereas patients with Alzheimer's disease and isolated extrapyramidal signs had scores in between both groups. Lastly, patients with Alzheimer's disease-parkinsonism showed a significantly higher frequency of both major depression and dysthymia than patients with Alzheimer's disease and no extrapyramidal signs.

Some limitations of our study should be pointed out. We classified patients into those with parkinsonism, isolated extrapyramidal signs, and no extrapyramidal signs based on the UPDRS scores, but more objective measurements of extrapyramidal signs were not assessed.² The only measure of dementia used in this study was the MMSE, and more appropriate measures, such as the CAMDEX,³² were not used. Finally, the neurological examination was not carried out blind to group membership, and the group of normal controls was small. We do not believe, however, that this may have influenced our present findings as we had no a priori hypothesis regarding the prevalence of extrapyramidal signs in Alzheimer's disease.

Molsa *et al*¹ reported that only 8% of a consecutive series of patients with Alzheimer's disease did not have extrapyramidal signs, but an age comparable control group was not

examined. Whereas our study showed that the prevalence of parkinsonism was significantly higher in the Alzheimer's disease group, the prevalence of isolated extrapyramidal signs was similar to that found in non-demented age comparable controls. Although future studies should examine the prevalence of extrapyramidal signs in young controls, this finding suggests that the high frequency of isolated extrapyramidal signs in patients with Alzheimer's disease is related to age and not to the presence of dementia. On the other hand parkinsonism (as defined in the present study) was a specific finding restricted to a subgroup of patients with Alzheimer's disease. Based on these findings, future studies that examine extrapyramidal signs in Alzheimer's disease should be restricted to patients with Alzheimer's disease with tremor or rigidity and bradykinesia. It should also be stressed that, in agreement with a recent report by Kischka *et al*,³³ we found that rigidity and akinesia but not tremor were the most prevalent extrapyramidal signs in patients with Alzheimer's disease and parkinsonism.

Another finding of our study was the significant association between depression and extrapyramidal signs in Alzheimer's disease. Extrapyramidal signs have also been reported in patients with primary (no known brain injury) depression. In a study that examined the presence of extrapyramidal signs in non-depressed patients with Parkinson's disease, primary depression, and normal controls, Rogers *et al* found that depressed patients had significantly more extrapyramidal signs than normal controls (significantly higher scores on the Webster scale).³⁴ These signs improved after depressed patients were successfully treated with antidepressant medications. Few studies have examined the neuropathological correlates of depression in patients with Alzheimer's disease. Zweig *et al*³⁵ reported a significantly greater neuronal loss in both the locus coeruleus (which provides noradrenergic innervation to most of the cortex) and the dorsal raphe nuclei (where serotonergic neurons are located) in patients with Alzheimer's disease and depression compared with non-depressed patients with Alzheimer's disease. Zubenko *et al*³⁶ confirmed the significant neuronal depletion in the raphe nuclei of depressed patients with Alzheimer's disease, but they also reported a significant neuronal loss in the substantia nigra of depressed compared with non-depressed patients with Alzheimer's disease. In a recent study, Forstl *et al*³⁷ reported a significant association between loss of noradrenergic and cholinergic neurons and depression scores in Alzheimer's disease. Thus it is possible that the association between depression and extrapyramidal signs found in the present study may result from significant depletions of biogenic amines.

In a recent study, Girling and Berrios¹³ examined the association between extrapyramidal signs and cognitive deficits in Alzheimer's disease, and found a significant correlation between higher scores on the Webster scale and more deficits on the con-

trolled oral-word association test, a test considered to be sensitive to frontal lobe dysfunction. Our study had methodological improvements compared with the report of Girling and Berrios because we excluded patients taking neuroleptics or other medications that could potentially induce extrapyramidal signs, and we assessed patients with a more comprehensive neuropsychological battery. Although patients with and without extrapyramidal signs did not show significant differences on the MMSE (a measure of global cognitive decline), patients with Alzheimer's disease-parkinsonism showed significant deficits in frontal lobe-related tasks, such as the Wisconsin card sorting and the trail making tests (which measure shifting abilities), the controlled oral word association test (which measures verbal fluency), and the Raven's progressive matrices (which assesses abstract reasoning). We also found significantly more severe constructional apraxia in patients with Alzheimer's disease-parkinsonism, which some authors consider may also be present in patients with frontal lobe related deficits.⁴⁰ Whereas significant between group differences in specific cognitive tasks may be related to the higher sensitivity of these tasks compared with the MMSE, no significant differences were found on verbal and visual memory tasks, which were reported to be the most sensitive tests for the diagnosis of dementia.³⁹ Thus our study replicates that of Girling and Berrios—namely, the finding of frontal lobe related cognitive deficits in patients with Alzheimer's disease and extrapyramidal signs. Moreover, we also found that deficits in frontal lobe related tasks mostly correlated with rigidity and bradykinesia, but not with tremor.

The question that now arises is what is the mechanism of parkinsonism in Alzheimer's disease? This question may be answered from clinical, neuropathological, and pharmacological perspectives. We have already discussed discrepancies between neuropathological and neuroradiological reports. Thus for the present study, we decided to examine the mechanism of extrapyramidal signs in Alzheimer's disease by a pharmacological approach (the apomorphine test). In patients with Parkinson's disease the administration of apomorphine is usually followed by a dramatic improvement in extrapyramidal signs.⁸ This indicates a good response to levodopa treatment, and may be a marker of presynaptic nigrostriatal dysfunction. In the present study none of the 11 patients with Alzheimer's disease and parkinsonism who underwent the apomorphine test showed a positive motor response, suggesting that parkinsonism in Alzheimer's disease may not result from nigrostriatal dysfunction. Another possibility is that the Alzheimer's disease-parkinsonism group has a diffuse Lewy body disease, as patients with this disease may show extrapyramidal signs that do not respond to dopaminergic agonists.⁴⁰ Several findings argue against this possibility. Perry *et al* described the clinical features of pathologically confirmed senile

dementia of the Lewy body type, and reported that the onset of illness was characterised by an acute or subacute confusional state, the extrapyramidal signs were mild, and patients did not meet the clinical criteria for probable Alzheimer's disease.³⁵ On the other hand all our patients with Alzheimer's disease-parkinsonism met the criteria for probable Alzheimer's disease, and none of them had delirium at the onset of dementia. Regardless of the final neuropathological outcome, we find a significant association between parkinsonism in Alzheimer's disease and specific psychiatric and cognitive changes.

In conclusion, we found that about one quarter of a consecutive series of patients with Alzheimer's disease had parkinsonism. These patients did not improve from their motor deficits with dopaminergic agonists, and showed a high frequency of depression. Patients with Alzheimer's disease and parkinsonism had significantly more severe deficits in frontal lobe related tasks and constructional praxis than patients with Alzheimer's disease but without parkinsonism. Whether the parkinsonism in Alzheimer's disease improves after treatment with antidepressant drugs, and whether this subgroup of patients with Alzheimer's disease show metabolic deficits in specific brain areas will have to be examined in future studies.

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