Extrapyramidal symptoms and signs in Alzheimer's disease: Prevalence and correlation with the first symptom

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Abstract

Objectives: *To determine the prevalence and clinical correlates of extrapyramidal signs (EPS) in outpatients with probable Alzheimer's disease (AD); to examine the appearance of EPS in association with the first symptom that led the patient or family to ask for medical help; to examine the association of the prevalence of EPS with gender, age at onset of the disease, duration of the disease, severity of dementia, functional disability, and potential use of neuroleptics; and to address the issue of the possible role of EPS as a predictive factor for the clinical course of the disease.*

Patients and methods: *We examined 126 patients meeting NINCDS-ADRDA* criteria for probable AD and 29 healthy, nondementia controls of comparable age and gender. Thirteen of the patients taking neuroleptics at the time of the examination were excluded from the main study group and formed a separate subgroup of AD/neuroleptics-positive. Twenty-eight of the AD/neuroleptics-free patients were re-examined during an 18-month period in order to determine the possible role of EPS as a predictive factor of the clinical course of the disease.*

Results: *Only 8 percent of the AD/neuroleptics-free patients were free of EPS, while the corresponding percentage in the control group was 61.5 percent. The most common types of EPS presented in the patient group were hypomimia ([facial mask] 60 percent), difficulty in talking (53.66 percent), bradykinesia (51.4 percent), postural instability (47.33 percent), abnormal gait (34.66), and rigidity (26 percent), respectively. No significant differences were found when examining for the presence of resting tremor, other tremors, dystonias, and dyskinesias. With regard to the presence of EPS and the first symptom, no significant difference was found among patients whose first complaint was memory disorder (probable AD) and patients with other symptoms. When examining the association between the prevalence of EPS and gender or age at onset of the disease, no special correlation was detected. However, such a correlation was found between the prevalence of EPS and duration of the disease, as indicated by the fact that EPS appear in 78.9 percent of the patients with a duration of illness less than two years, but in 97 percent of the patients with a corresponding duration of two years or more. The mean duration of the disease in patients*

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appearing with EPS is found to be 2.68 ± 1.98 years. The presence of EPS increases proportionally with the progression of the disease and cognitive and functional decline. Patients with poor results in the MMSE (score of less than 11) appear to present EPS at a greater percentage than those with better performance on the examination (MMSE scores greater than 11). With regard to the association between EPS and functional ability in AD, it seems that the presence of EPS imposes difficulties in daily activities, as seen by the fact that patients with EPS have lower FRSSD scores (mean ± SD: 14.87 ± 10.53) than patients without EPS (5 ± 2.58). After controlling for duration of the disease, the use of neuroleptics is found to influence the appearance of EPS in patients with AD. Almost all of the patients AD/neuroleptics-positive patients presented EPS (100 percent), while 92 percent of the AD/neuroleptics-free patients manifested such symptoms.

Finally, we re-evaluated 28 patients, who were part of the initial AD/neuroleptics-free group, in order to determine whether the appearance of EPS could have prognostic value for the clinical course of the disease. Patients who presented EPS at initial examination appeared to deteriorate faster, mainly cognitively, but also functionally. The mean decrease in MMSE scores in patients with EPS was found to be 2.65 ± 3.46; while in patients without EPS at initial visit, MMSE scores were 0.63 ± 3.88. The functional decline seems to be less influenced by the presence of EPS. The corresponding mean decrease in FRSSD scores of the two groups was 2.1 ± 5.55 and 1.8 ± 2.1, respectively.

Key words: Alzheimer's disease (AD), extrapyramidal signs (EPS), neuroleptics

Introduction

Progressive deterioration of memory and other cognitive functions is the principal feature of Alzheimer's disease (AD). However, patients with dementia of the Alzheimer's type often exhibit additional signs of cerebral dysfunction, such as extrapyramidal signs (EPS), which become more prevalent as the disease progresses.

Several studies have confirmed the presence of EPS in Alzheimer's disease and the cross-sectional frequencies for overall EPS in these reports ranges from 6 percent to 90 percent.[1,2,11,16,21,23-26,28,30,32,34,36] There are studies providing data on individual signs of Parkinsonism, while others reported only the overall frequency of EPS. Among the most frequent Parkinsonian signs found in patients with AD were bradykinesia, facial masking, speech abnormalities, rigidity, postural instability, and gait disorders, while resting tremor, other tremors, dystonias, and dyskinesias were distinctly uncommon.[2,16,23,26,30,34]

With regard to the influence of age on the prevalence of EPS in AD patients, there are studies that suggest there is a slight one, while others have found no difference in age between Alzheimer's patients with EPS (AD/EPS+) and those without (AD/EPS-).[18,28,34] Similarly, there is low consistency among the findings of reports on the association of the prevalence of EPS and gender[11,28,30,32] or the duration of the disease.[16,23,28,32]

In reviewing the data on the prevalence of EPS in AD patients, one can assume that EPS are found more frequently in studies where patients using neuroleptics were included, suggesting that neuroleptic use affects the appearance of EPS, although the extent of such an influence has not been fully evaluated.[30]

Additionally, EPS have been associated with severe intellectual decline or early loss of abilities in daily activities, whereas other studies failed to ascertain such an association.[9,15,16,25,28-30,32]

Furthermore, EPS are cardinal features of the recently described Lewy-body variant of AD, which is clinically characterized by fluctuating cognitive impairment, visual hallucinations, impairment of consciousness, gait abnormalities, EPS, and rapid progression of the disease.[8,17,20,31] Also, although Alzheimer's and Parkinson's disease are generally held to be separate entities, a considerable amount of evidence exists (among which is the presence of EPS in AD) to demonstrate that these disorders share common clinical and neuropathologic features, and overlap between the two conditions is extensive and far greater than one would anticipate by chance alone. Thus, elimination of common clinical manifestations (*e.g.*, EPS) may answer the question of whether such overlap reflects a common spectrum of degeneration that preferentially affects specific neuronal populations in individual patients.[37]

Consequently, to study the presence and significance of EPS in patients with dementia of the Alzheimer's type is of great importance for better understanding of the presentation and clinical course of the disease.

Up to now, there has been much debate concerning these issues and the variability in the reported results across case series must be attributed to certain limitations, such as differences in characterization of cohorts with respect to neuroleptic use, assessment of EPS with clinically validated and standardized rating scales, the spectrum of extrapyramidal symptoms examined, and consistency of parallel examination of nondementia subjects.

In this study, we evaluated the prevalence of EPS in patients with probable Alzheimer's disease and nondementia controls of comparable age and gender.

A significant aim of the study was to evaluate whether the first symptom reported by the patient or family is crucial for the appearance of EPS.

Table 1. Demographic data		
	Patients AD/neuroleptics-free	**Control group**
	100	29
Gender (male/female)	31/69	9/20
Age (years)	70.58 ± 8.33	70.10 ± 7.96
Age at onset (years) (mean ± SD, range)	67.07 ± 7.81 (47 - 85)	
Duration of disease (years) (mean ± SD, range)	2.68 ± 2.22 (0.1 - 10)	
MMSE scores (mean ± SD, range)	15.44 ± 6.93 (0 - 27)	
CAMCOG scores (mean ± SD, range)	48.52 ± 22.09 (0 - 93)	

We also examined the association of the EPS presented with gender, age at onset of the disease, duration of the disease, severity of dementia, functional disability, and the potential role of neuroleptics.

In order to determine how the advent of EPS influences the progression of AD, we re-examined 28 AD/neuroleptics-free patients in an 18-month follow-up period.

Patients and methods

A consecutive series of 122 patients at external baseline were treated at the 3rd Neurology Clinic of Aristotle University of Thessaloniki because of progressive cognitive decline and were screened for inclusion in this study. They had been our patients for many years and were examined every three months. The inclusion criteria were:

- NINCDS-ADRDA* criteria for probable AD;
- No history of head injuries with loss of consciousness, stokes, or other neurological disorders with CNS involvement;
- Normal results on laboratory tests;
- No focal lesions on CT scan;
- No past or present intake of drugs that could produce EPS (*e.g.*, neuroleptics, calcium channel blockers, chronic use of antiemetics);
- No past or present use of l-dopa or dopamine agonists; and
- Cognitive decline preceded the appearance of EPS.

One hundred patients met the criteria and were included in this study, forming the AD/neuroleptics-free group. Thirteen patients taking neuroleptics at the time of the examination were excluded from the main study group and formed a separate AD/neuroleptics-positive subgroup. The prevalence of EPS in this subgroup was compared separately with the corresponding prevalence in the main study group (AD/neuroleptics-free). Nine patients were excluded entirely from the study because of other concomitant neurological disorders.

We also examined 29 healthy, nondementia subjects of comparable age and gender with no history of neurological or psychiatric disorders and no past or present intake of drugs that could produce EPS, l-dopa, or dopamine agonists. All patients and control group subjects received comprehensive medical, psychiatric, neurological, and neuropsychological examinations (*i.e.*, Mini-Mental State Examination [MMSE], Cambridge Cognitive Examination [CAMCOD], Geriatric Depression Scale [GDS], Hamilton Depression Scale, and Functional Rating Scale for Symptoms of Dementia [FRSSD]).

EPS were assessed using the Extrapyramidal Symptoms Rating Scale (ESRS) and the Unified Parkinson's Rating Scale (UPDRS). In the ESRS, each sign is rated as either *absent, mild, moderate*, or *severe* in section I, and *absent, borderline, very mild, mild, moderate, moderately severe, marked, severe*, and *extremely severe* in sections II to VII. In the UPDRS, each sign is rated as either absent (0), slight (1), mild-moderate (2), marked (3), or severe (4). Mild nonspecific symptoms were rated as 1. For all analyses, patients that had at least one sign

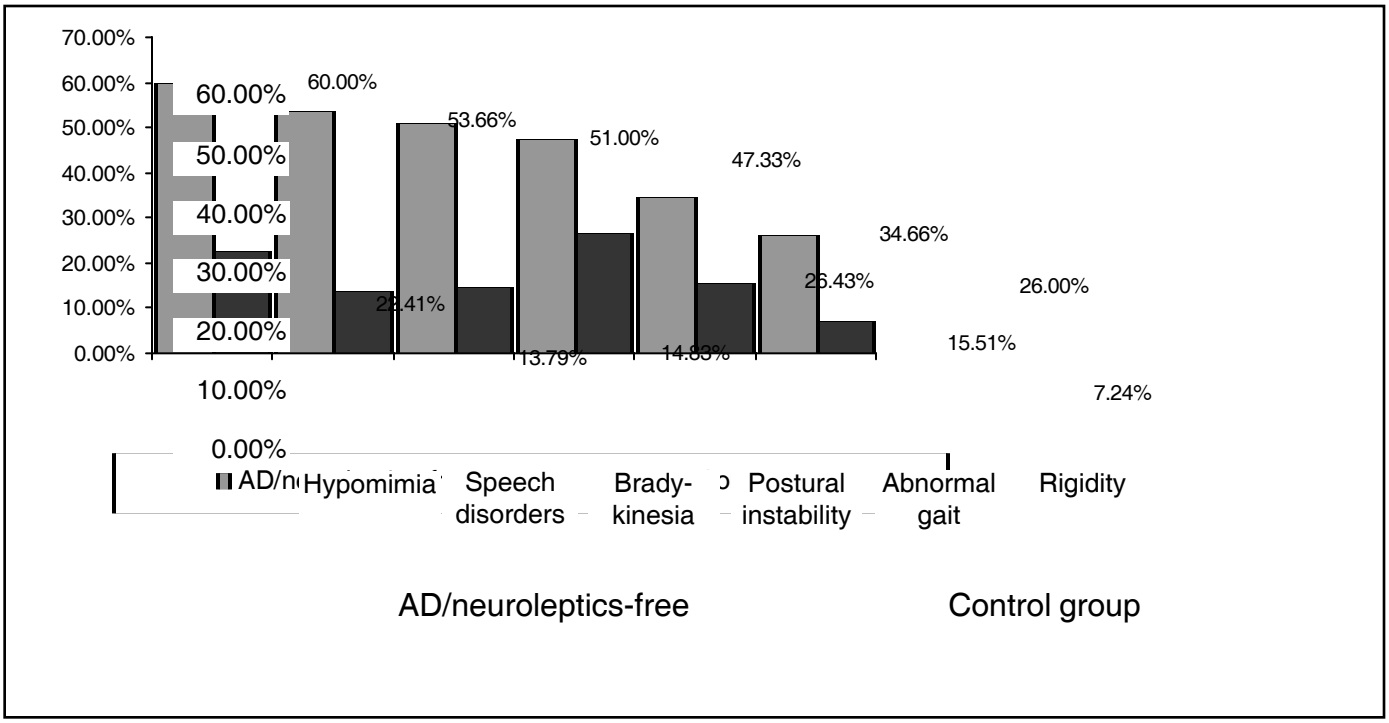

Figure 1. Presence of EPS in AD/neuroleptics-free patients and control subjects (statistically significant difference, $p < 0.05$).

rated as mild-moderate were considered to have EPS. We used this criterion because EPS ratings of this severity are more reliable and apt to be noticed by the average clinician. Inter-rater reliability for this scale has already been established.[13] Functional capacity was rated by using the FRSSD. In this scale, the higher the score is, the greater is the impairment. All patients were assessed with the MMSE, an 11-item examination that has been found reliable and valid in assessing a limited range of cognitive function in patients with dementia. Characterization of dementia into two categories (mild to moderate and marked to severe) was based on an interview with the patient and the MMSE (patients with MMSE scores of more than 11 formed the first subgroup and patients with MMSE scores of less than 11 formed the second subgroup).

No statistically significant differences between the two studied groups (patients/neuroleptics-free and controls) were found for age and gender. The mean age of patients with AD was 70.58 ± 8.33, while the mean age of the control group was 70.10 ± 7.96. There were 31 men and 69 women in the patient group, and nine men and 20 women in the control group. The mean MMSE score for the AD patients was 15.44 ± 6.93, while their mean score on the CAMCOG was 48.52 ± 22.09. The mean age of onset was 67.07 ± 7.98, while the mean duration of illness for the patients examined was 2.68 ± 2.22 (Table 1).

Table 2. Types of EPS without statistically significant difference of presence ($p > 0.05$) in AD/neuroleptics-free patients and control group

	Patients AD/neuroleptics-free (%)	Control group (%)
Resting tremor	21.4	14.03
Other tremors	48.5	32.76
Dyskinesias	4.72	0
Dystonias	0	0

Table 3.Types of EPS with statistically significant difference of presence ($p < 0.05$) in patients with AD and control group		
	Patients Neuroleptics-free (%)	**Control group (%)**
Hypomimia (facial mask)	60	22.44
Difficulty in talking	53.66	13.79
Bradykinesia	51.4	14.83
Postural instability	47.33	26.43
Abnormal gait	34.66	15.51
Rigidity	26	7.24

Results

EPS were observed in most patients with AD, but in a minority of the control group subjects. Only eight patients (8 percent) were free of EPS, while the corresponding percentage of the control group was 61.5 percent. The most common type of EPS found in patients with AD was hypomimia (facial mask), speech disorders, bradykinesia, postural instability, rigidity, and abnormal gait (Figure 1).

No significant differences were found in examining the presence of resting tremor, other tremors, dyskinesias, and dystonias (Table 2).

Hypomimia (facial mask) was found in 60 percent of the patients (mild: 35.5 percent; moderate: 21.5 percent; severe: 3 percent), while the corresponding percentage of the control group was 22.41 percent, with almost all subjects showing a mild degree of the symptom.

Difficulty in talking with low, monotonous speech, sometimes slurred or even unintelligible, was found in 53.66 percent (mild: 30.67 percent; moderate: 14.67 percent; severe: 8 percent), but in only 13.79 percent of the control group. Bradykinesia was present in 51.4 percent of the patients (mild: 25.9 percent; moderate: 18 percent; severe: 7.5 percent). Patients with severe bradykinesia showed great difficulty in starting or stopping any voluntary movement. The corresponding percentage of the control group was 14.83 percent. Postural instability was detected in 47.33 percent of the patients with AD (mild: 28 percent; moderate: 14.67 percent; severe: 4.34 percent), and in 26.43 percent of the control group, most of them manifesting mild postural instability. Abnormal gait was present in 34.66 percent of the patients (mild: 19.84; moderate: 11.34 percent; severe: 3.5 percent) and in 15.51 percent of the control group. Rigidity was usually found symmetrically in arms, legs, and neck in 26 percent of the patients (mild: 17.1 percent; moderate: 5.3 percent; severe: 3.6 percent). Only 7.24 percent of the control group appeared with mild rigidity, also symmetrically (Table 3).

As we can see, the total prevalence of EPS, as well as the prevalence of individual EPS, is significantly higher in the AD group. Moreover, the EPS are found to be of greater severity (Table 4).

When we examined the association between the prevalence of EPS and gender or age at onset of the disease, we did not detect any special correlation (Table 5).

For patients with early onset of the disease (< 65 years), 89.5 percent presented with EPS, which was similar to the percentage found for those with late onset (Table 6).

With regard to the first symptom of cognitive impairment reported by the patient or family, no difference was detected between patients that manifested EPS and those that did not. With regard to the presence of EPS and the first symptom, no significant difference was found among patients whose first complaint was memory disorder (probable AD) and those with behavioral problems (probable Lewy-body disease), visuospatial dysfunction (parietal lobe), language disorders (primary progressive aphasia), or executive dysfunction (frontal dementia) as first symptom.

The prevalence of EPS was similar both in the subgroup of patients who reported memory disorder as first symptom of the disease and in the subgroup of patients (13) whose first symptom was other than memory deficits (*i.e.*, behavioral problems, space disorientation, executive disorders, or language disorders) (Table 7).

Upon analysis of the association of EPS frequency with duration of the disease, we reached the conclusion

Table 4. Severity of EPS in AD/neuroleptics-free patients and control subjects						
	AD/neuroleptics-free patients (%)			Control group (%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Hypomimia	35.5	21.5	3	15.51	6.89	0
Difficulty in talking	30.67	14.67	8	9.19	4.59	0
Bradykinesia	25.9	18	7.5	6.89	6.55	1.38
Postural instability	28	14.67	4.34	18.39	8.05	0
Abnormal gait	19.84	11.34	3.5	8.62	6.32	0.57
Rigidity	17.1	5.3	3.6	5.86	0.34	1.04

that EPS tend to increase as the disease progresses, as seen by the fact that they were more prevalent in the subgroup of patients whose duration of illness was more than two years (Table 8).

The mean duration of the disease in the group of patients presenting EPS was 2.68 years ± 1.98. However, our study is not longitudinal; therefore, we cannot exclude the possibility that EPS have been present before our examination, thus occurring in an even earlier stage of the disease. This would make the advent of EPS in AD quite useful as a predicting factor of the clinical course if such a role were established, something under trial in several studies. When examining the presence of EPS in association with the severity of dementia, it becomes clear that, as the disease progresses and the cognitive impairment worsens, the prevalence of EPS increases. Patients with poor results in the MMSE (score of less than 11) appear to present EPS at a greater percentage than those with better performance on the MMSE (score greater than 11) [Table 9(a)].

With regard to the association between EPS and functional ability in AD, it seems that the presence of EPS imposes difficulties in daily activities, as seen by the fact that patients with EPS have higher FRSSD scores (mean ± SD: 14.87 ± 10.53) than patients without EPS (5 ± 2.58).

Thirteen patients from the original group, who were taking neuroleptics at the time of examination, were initially excluded from the study, forming a separate AD/neuroleptics-positive subgroup. We examined the prevalence of EPS in these patients as compared with the AD/neuroleptics-free patients. The results suggest that the use of neuroleptics in patients with dementia of the Alzheimer's type has little effect on the appearance of EPS [Tables 9(b) and 10, Figure 2].

Twenty-eight patients who were part of the initial AD/neuroleptics-free group were re-examined during an 18-month follow-up period. Patients who presented EPS at initial examination appeared to deteriorate faster, mainly cognitively, but also functionally. The mean decrease in MMSE scores in patients with EPS was found to be 2.65 ± 3.46, while in patients without EPS at initial visit the mean decrease was 0.63 ± 3.88. The functional decline seems to be less influenced by the presence of EPS. The corresponding mean decrease in FRSSD scores of the two groups was 2.1 ± 5.55 and 1.8 ± 2.1, respectively.

Table 5. Prevalence of EPS associated with gender (no significant difference, p > 0.05)		
Gender	Patients with EPS (%)	Controls with EPS (%)
Male (N = 31/9)	87.1	66.7
Female (N = 69/20)	97.0	65.0

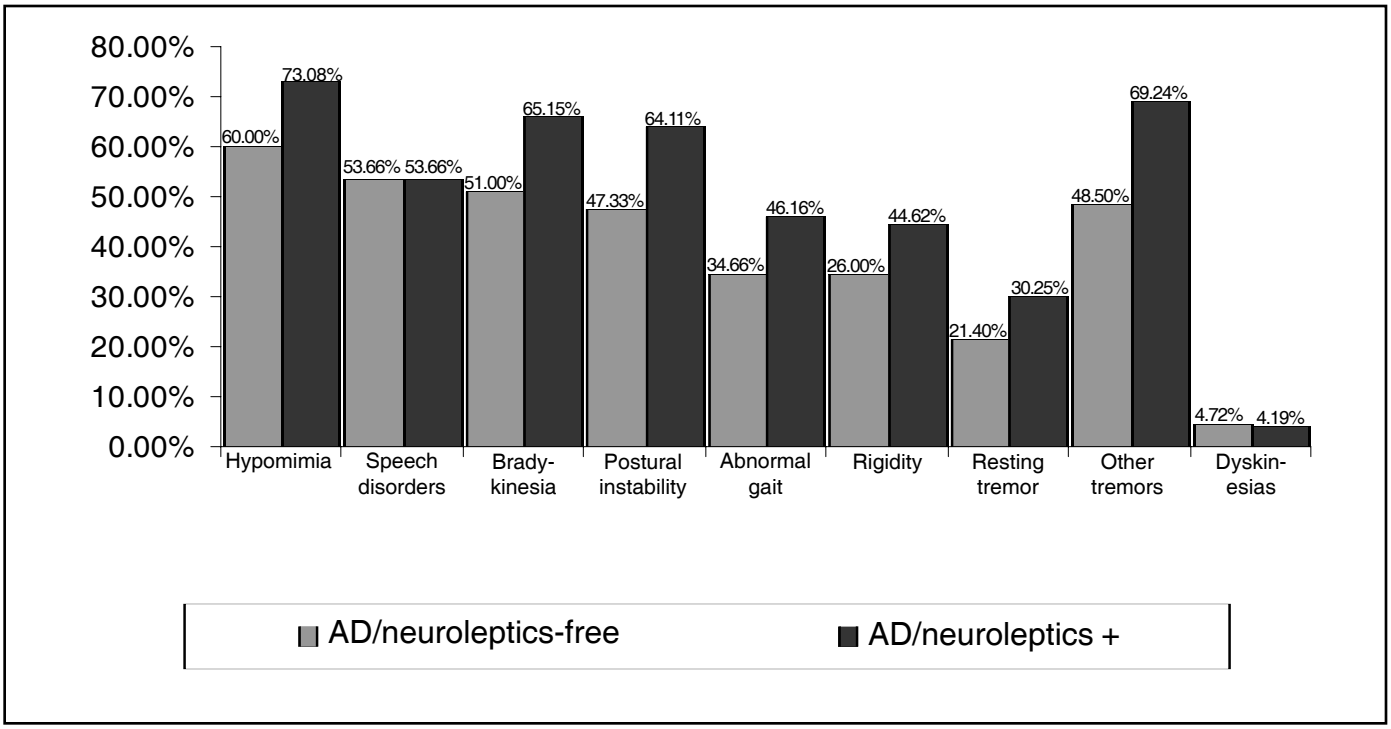

Figure 2. Prevalence of EPS in AD/neuroleptics-positive and AD/neuroleptics-free patients.

Discussion

This study examined the prevalence, clinical correlates with the first symptom, and potential prognostic value of EPS in patients with probable Alzheimer's disease. We also inquired whether the first symptom reported by the patient or family had a specific correlation with the more frequent appearance of EPS in the clinical course of the disease.

Only 8 percent of the AD/neuroleptics-free patients were free of EPS, while the corresponding percentage of the control group was 61.5 percent. Molsa *et al.*[2] also found an identical percentage of patients free of extrapyramidal symptomatology (8 percent). However, in the latter study, a group of nondementia, age- and gender-comparable, healthy controls was not assessed. Differences between our results and those reported by other studies,[1,2,11,16,21,23-26,28,30,32,34,36] although not dramatic, must be attributed to differences in the characterization of cohorts with respect to neuroleptics use, assessment of EPS with standardized rating scales, spectrum of Parkinsonian symptomatology examined, and source of patients included in the study.

The most common types of EPS found in patients with AD were hypomimia (facial mask), speed disorders, bradykinesia, postural instability, abnormal gait, and rigidity, while no significant differences were found while examining the presence of resting tremor, other tremors, dyskinesias, and dystonias. These findings are consistent with those of other studies, reporting that tremor, dyskinesias, and dystonias are rare in patients with AD.[2,16,23,26,30,34]

Table 6. Prevalence of EPS associated with age at onset (no significant difference, p > 0.05)

Age at onset	Patients with AD (N)	Prevalence of EPS (%)
< 65 years	37	89.5
> 65 years	63	90.9

Table 7. Prevalence of EPS according to the first symptom reported (no significant difference, p < 0.05%)		
	Memory disorders (%) (n = 100)	**Other problems (%) (n = 13)**
Hypomimia	64.01	65.38
Difficulty in talking	53.17	65.38
Bradykinesia	53.49	58.46
Postural instability	46.03	53.84
Abnormal gait	33.86	35.89
Rigidity	25.07	36.16

With regard to the presence of EPS and the first symptom that led the patient to the doctor, no significant difference was found among patients whose first complaint was memory disorder and those with behavioral problems, spatial disorientation, language disorders, or executive disorders as first symptom. This finding may indicate that EPS in AD cannot be specifically connected to a certain cognitive deficit; thus being a somewhat constant characteristic of the clinical picture of the disease. Consequently, this appraisal enhances a recently argued and much debated theory that AD and Parkinson's disease are not distinct diseases entities, but rather they constitute the phenotypical continuum of a common degenerative procedure, which preferentially affects specific neuronal populations in individuals.[37]

Perhaps, although neurodegeneration in degenerative diseases (including Alzheimer's disease, Parkinson's disease, primary progressive aphasia, Lewy-body disease, and frontotemporal dementia) starts from different parts of the brain (such as entorrhinal cortex, hippocamus, substance negra, perisylvian region of the left hemisphere, parietal lobe, or frontal lobe), the final result is the same: dementia and motor symptoms. Either the degenerative disease that causes dementia has prominent motor symptoms (*e.g.*, Parkinson's, Huntington's, Hallervorden-Spatz disease, and corticobasalganglionic degeneration) or is without prominent motor symptoms at the beginning (Alzheimer's, Pick's disease, focal nonspecific degeneration, cortical Lewy-body disease, Jacob Creutzfeld disease), but, ultimately, the re result is the same.

Gender or age at onset of the disease were found to have no significant influence in the appearance of EPS, a finding also confirmed by other studies.[28,30,32]

Although several studies found no special correlation between the appearance of EPS and duration of disease, longitudinal studies report that EPS become more frequent as the disease progresses over time.[16,25,29,30] One actuarial study suggested that, with careful observation, EPS are eventually noted in *all* patients with AD.[38] In our study, patients with duration of illness of more than two years presented EPS at a higher percentage than

Table 8. Prevalence of EPS associated with the duration of the disease		
Duration of illness	**Patient with AD (N)**	**Prevalence of EPS (%)**
> 2 years	37	78.9
< 2 years	63	97.0

Table 9(a). Prevalence of EPS in AD/neuroleptics-free patients according to the severity of the disease		
	Mild to moderate (%)	**Marked to severe (%)**
Hypomimia	53.58	75
Difficulty in talking	48.1	77.78
Bradykinesia	45	75.56
Postural instability	44.29	70.38
Abnormal gait	31.43	50
Rigidity	23.13	35.55

patients with a corresponding duration of less than two years.

After controlling for duration of the disease, the use of neuroleptics is found to influence the appearance of EPS in patients with AD. Almost all of the AD/neuroleptics-positive patients presented EPS (100 percent), while 92 percent of the AD/neuroleptics-free patients manifested such symptoms. However, the prevalence of extrapyramidal symptomatology in AD is far higher than can be attributed to neuroleptic use alone.

EPS are found more frequently in patients with low MMSE and high FRSSD scores, implying that extrapyramidal involvement becomes more prevalent as the disease progresses and cognitive and functional abilities decline. Additionally, when we re-examined a subgroup of AD/neuroleptics-free patients, we found that those

Table 9(b). Prevalence of EPS in AD/neuroleptics-positive and AD/neuroleptics-free patients		
	AD/neuroleptics positive patients (%)	**AD/neuroleptics-free patients (%)**
Hypomimia	73.08	60
Difficulty in talking	53.66	53.66
Bradykinesia	66.15	51.4
Postural instability	64.11	47.33
Abnormal gait	46.20	34.66
Rigidity	44.62	26
Resting tremor	30.25	21.4
Other tremor	69.24	48.5
Dyskinesias	4.90	4.72

Table 10. Severity of EPS in AD/neuroleptics-positive and AD/neuroleptics-free patients						
	AD/neuroleptics-positive patients (%)			AD/neuroleptics-free patients (%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Hypomimia	30.76	30.76	11.54	35.5	21.5	3
Difficulty in talking	30.76	14.67	8	30.67	14.67	8
Bradykinesia	21.54	24.62	14.62	25.9	18	7.5
Postural instability	35.89	20.52	7.69	28	14.67	4.34
Abnormal gait	25.64	14.11	6.41	19.84	11.34	3.5
Rigidity	16.16	16.92	11.54	17.1	5.3	3.6
Resting tremor	23.07	6.67	0	14.94	5.34	1.14
Other tremors	42.31	26.92	0	35	12.5	1
Dyskinesias	18.22	1.89	0	4.72	0	0

who presented EPS at initial examination appeared to deteriorate faster, mainly cognitively, but also functionally. The mean decrease in MMSE scores in patients with EPS was found to be 2.65 ± 3.46, while in patients without EPS at initial visit it was 0.63 ± 3.88. The functional decline seems to be less influenced by the presence of EPS. The corresponding mean decrease in FRSSD scores of the two groups was 2.1 ± 5.55 and 1.8 ± 2.1, respectively. This study supports earlier notions of the prognostic value of EPS in AD.[16,25,28,30]

In conclusion, this study tried to establish a relative reliability of the reported results by (a) using a control group consisting of nondementia subjects of comparable age and gender; (b) assessing EPS with clinically validated and standardized rating scales (UPDRS-ESRS); (c) providing data on individual signs of Parkinsonism along with the overall frequency of EPS, as well as evaluating the degree of each sign reported; (d) excluding patients taking neuroleptics from the initial study group and separately studying the prevalence of EPS in this subgroup. However, a limitation of this study is that the follow-up period has not yet been carried out extensively, with the future prospect of including a larger number of re-examined patients and adapting the study in terms of duration of follow-up and selected terminal endpoints in order to extract more valid and reliable results.

Finally, although the increased prevalence of EPS in AD is repeatedly confirmed, their true nature remains to be clarified. Thus, unanswered questions arise, such as whether EPS (a) simply represent a particular stage in the natural history of the disease; (b) signify the possibility of a second neurodegenerative disorder; or (c) reflect a distinct pathologic subtype of the disease, usually referred to as the Lewy-body variant of AD. Answers to these questions demand assessing the issue from clinical, neuropathological, and pharmacological perspectives, which remains to be done in future studies.

Note

**National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer Disease and Related Disorders Association.*

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