ORIGINAL CONTRIBUTION

Extrapyramidal Signs Before and After Diagnosis of Incident Alzheimer Disease in a Prospective Population Study

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Background: Extrapyramidal signs (EPSs) are commonly accepted as a feature of Alzheimer disease (AD) and may influence both the profile of impairment and prognosis.

Objective: To examine rates of occurrence and risk factors for all types of EPSs and to describe the impact of EPSs over time on the clinical course of AD.

Design: Longitudinal study.

Setting: The Washington Heights Hamilton Heights Inwood Columbia Aging Project.

Patients: A total of 388 patients with incident AD (mean age, 79 years; 71.4% female).

Main Outcome Measures: Extrapyramidal signs rated by means of a standardized portion of the Unified Parkinson's Disease Rating Scale; prevalence and incidence rates and cumulative risk for non–drug-induced EPSs; and rates of change in EPSs over time, taking into account potential covariates.

Results: Extrapyramidal signs were detected in 12.3% of patients at first evaluation and 22.6% at last evaluation. In a multivariate-adjusted generalized estimating equation model of change, total EPS score increased at an annual rate of 1.3%. Women (relative risk [RR], 1.57; $P=.03$), older patients (RR, 1.03; $P=.02$), and those with EPSs at baseline (RR, 2.07; $P=.001$) had greater rates of cognitive decline.

Conclusions: Extrapyramidal signs occur frequently and progress significantly in AD. Patients with incident AD and concomitant EPSs have a greater rate of cognitive decline than do patients with incident AD but without EPSs.

Arch Neurol. 2009;66(9):1120-1126

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THE FREQUENCY AND SEVERITY of extrapyramidal signs (EPSs), a common feature of Alzheimer disease (AD), appear to increase over time with disease severity.[1] However, the clinical significance of EPSs is poorly understood because EPSs may result from different underlying mechanisms and location or type of lesions. At a clinical level, they appear to influence both profile of impairment and prognosis, with several studies showing an association between increased EPSs and more severe cognitive impairment, rapid cognitive decline, institutionalization, higher total annual cost, and death.[2-9]

Most but not all previous studies were conducted in clinic-referred patients but not in population-based cohorts. Differences between studies with regard to diagnostic criteria and population sampling have led to considerable variability in prevalence estimates, which range from 6% to more than 50%.[1] Prospective studies of EPSs have been rare and have generally focused on changes in specific EPSs in individuals with established AD. Little is currently known about the temporal relationship between EPSs and AD onset, the relative frequency of different EPSs, risk factors for different EPS profiles, or the manner in which specific EPSs may modulate clinical presentation.[8,10,11]

The present study is based on a community-based, prospectively observed cohort of incident AD cases with baseline examinations before diagnosis. The rationale was based on the following considerations: (1) the pathological changes of AD are present in the brain many years before the clinical onset of symptoms of dementia, (2) patients with AD may exhibit evidence of motor symptoms before clinical diagnosis of dementia, and (3) rates of cognitive decline for patients with incident AD in our study were similar before and after clinical diagnosis of dementia. The study aimed to examine rates of occurrence and risk factors for all types of

EPSs, and to describe the impact of EPSs on the rate of the cognitive decline in a population-based cohort in which the date of onset of dementia is known.

METHODS

PARTICIPANTS

Subjects for the present study were recruited as part of the Washington Heights Hamilton Heights Inwood Columbia Aging Project and enrolled starting in 1992. This cohort consists of elderly individuals identified from a probability sample of Medicare beneficiaries who resided in an area of 3 contiguous census tracts in northern Manhattan. Access to the names of individuals was provided by the Health Care Financing Administration (now the Centers for Medicare and Medicaid Services). The proportion of individuals within each ethnic group and age stratum who participated in the study did not differ significantly from the source population. The study methodology is reported in detail elsewhere.[12]

The present study is based on individuals diagnosed as having incident AD in the course of the follow-up, but who did not have AD at baseline. We did not include individuals whose last evaluation was the incidence one, but only those for whom we had follow-up information after incidence. Three hundred eighty-nine individuals from the initial cohort study met these criteria.

PROCEDURES

The study cohort was followed up during a 14-year period beginning in 1992, during which time each participant received the same medical, neurologic, and neuropsychological evaluations. A physician elicited the medical and neurologic history of each person and conducted a standardized physical and neurologic examination. All ancillary information (medical records, clinical information, computed tomographic scans, or magnetic resonance images) was considered in the evaluation, if available. Medical diagnoses were assigned when applicable. This examination was repeated at each follow-up. Medical history was recorded with specific attention to stroke, trauma, medications, and recreational drug use. The medical comorbidities of participants were computed by means of a modified version of the Charlson Index of Comorbidity, which assessed conditions such as myocardial infarction, congestive heart failure, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, arthritis, gastrointestinal disease, mild liver disease, diabetes, chronic renal disease, and systemic malignant disease.

A standardized neuropsychological battery comprising evaluation of memory, orientation, abstract reasoning, language, and visuospatial abilities was administered to all participants at each follow-up. The test battery included the Selective Reminding Test,[13] the Benton Visual Retention Test,[14] orientation items from the modified Mini-Mental State Examination; the Boston Naming Test,[15] verbal fluency by use of the Controlled Oral Word Association Test, the Boston Diagnostic Aphasia Examination, the Complex Ideational Material and Repetition subtests, the Wechsler Adult Intelligence Scales–Revised Similarities subtest, the Mattis Dementia Rating Scale–Identities and Oddities subtest, the Rosen Drawing Test, and the Benton Visual Retention Test. Participants were tested in English or Spanish according to their preference.

Participants performing below specified cutoff scores for 2 memory measures and in 2 other cognitive domains were considered to have sufficient cognitive impairment to meet cognitive criteria for suspected AD. These cutoff scores have previously been shown to differentiate healthy control subjects and patients with dementia.[16] In addition to impaired cognitive performance, the diagnosis of AD required impairment in social or occupational functioning in accordance with the *Diagnostic and Statistical Manual of Mental Disorders*.[17] The longitudinal study design also permitted retrospective correction of initial AD diagnosis. Extrapyramidal signs were assessed by trained examiners by means of a modified Unified Parkinson's Disease Rating Scale, for which interrater reliability has already been established.[9,18]

Eleven EPSs (speech, tremor at rest [in any limb], facial expression, neck rigidity, right arm rigidity, left arm rigidity, right leg rigidity, left leg rigidity, posture, gait, and body bradykinesia/hypokinesia) were rated on a scale of 0 to 4, with 0 being normal and 4 indicating maximum impairment. These 11 items were then grouped into 5 domains[9]: speech/facial expression (2 items; score range, 0-8), tremor (1 item; range, 0-4), rigidity (5 items; range, 0-20), posture/gait (2 items; range, 0-8), and bradykinesia (1 item; range, 0-4). A total dichotomous EPS score was also calculated (total score ≥ 2 vs total score < 2) as an indicator of severity for which interrater reliability has been demonstrated in previous studies.[18] A continuous total score was also derived from the sum of all EPS severity scores (range, 0-44). A dichotomous form (< 2 or ≥ 2) and continuous score were also calculated for each domain subscore. Drug-induced EPSs were excluded from the analyses.

Information derived from the neurologic, psychiatric, and neuropsychological assessments at each follow-up was reviewed by an expert consensus group comprised of neurologists and neuropsychologists. On the basis of this review, all participants were assigned to 1 of 3 categories: dementia, mild cognitive impairment, or normal cognitive function. Only participants who did not have dementia at first evaluation and who developed AD at follow-up (incident AD) were included in this study. All procedures were approved by the institutional review board at Columbia University Medical Center.

STATISTICAL ANALYSES

Baseline characteristics of patients who did and those who did not reach the outcomes of interest during the study period were compared by means of the *t* test for continuous variables and χ^2 test for categorical variables. We calculated the prevalence of each EPS domain at baseline, time of incidence, and last visit.

Given the clustered nature of the data, and to use the full range of EPS scores and characterize rates of EPS change, we used generalized estimating equations,[19] which take into account multiple visits per patient and correlations owing to repeated examinations. The repeated measures for each patient are treated as a cluster. For each domain, total continuous EPS scores were entered as the dependent variable. The main independent variable was time (years since the initial evaluation). A significant time effect indicates significant changes of EPS score over time. Models also controlled for age at baseline, sex, education in years, and ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other).

To determine predictors of incident EPSs, we used Cox proportional hazards analysis with total EPSs (dichotomous form) as the outcome and duration (in years) between the initial visit and either development of EPSs or last evaluation without EPSs as the timing variable. Patients with EPSs at the first evaluation were not included in the Cox analyses. The following predictors were included in the model: age at entry into the study, sex, education in years, initial composite cognitive score, ethnicity (non-Hispanic, African American, and Hispanic), and apolipoprotein E genotype. We calculated similar Cox models for each EPS domain.

To characterize rates of cognitive changes, we also applied generalized estimation equations to the composite cognitive score. The composite cognitive measure was derived as fol-

lows: each of the 12 raw scores was transformed into a *z* score by means of means and standard deviations of scores from 272 controls without dementia in the Washington Heights Hamilton Heights Inwood Columbia Aging Project with a similar distribution of age, education, and ethnicity to the patients with AD. The *z* scores from individual tests were then averaged to create a *z* score for each cognitive domain. If more than half of the tests were missing, the domain score was considered missing and excluded from the analysis. The composite *z* score was derived by averaging 5 domain scores (memory, abstract reasoning, visuospatial skills, language, and executive speed), with missing data treated in the manner described earlier. The composite cognitive score was entered as the dependent variable. Independent variables were EPSs (dichotomous form), time (years from first evaluation or at time of incidence), and EPS × time interaction. A significant EPS effect would suggest a difference in cognitive performances at initial diagnosis for different EPS levels. A significant time effect would suggest a change in cognitive scores over time. A significant interaction term would suggest differential rates of cognitive change for different EPS levels. Models also adjusted for age at baseline, sex, education, and ethnicity.

Finally, to determine predictors of cognitive decline, we used Cox proportional hazards analysis with composite cognitive score as the outcome and duration (in years) between the initial visit and either development of composite cognitive score less than or equal to 1.5 or the last evaluation without a composite cognitive score less than or equal to 1.5 as the timing variable. Patients with a composite cognitive score less than or equal to 1.5 at the first evaluation were not included in the Cox analyses. The following predictors were included in the model: age at entry into the study, sex, education in years, initial EPS score, and ethnicity.

Table 1. Demographic and Clinical Characteristics

Characteristic	Finding
Age, mean (SD), y	
At baseline	79.18 (6.91)
At diagnosis of dementia	82.78 (6.93)
Sex, No. (%)	
Male	111 (28.6)
Female	277 (71.4)
Education, mean (SD), y	6.9 (4.6)
≥1 *APOE* E4* allele (n=322), % of patients	31.9
Duration of follow-up, mean (SD), y	3.6 (2.6)
No. of visits, mean (SD)	4.1 (1.8)
No. of visits after diagnosis of dementia, mean (SD)	2.7 (1.3)
Ethnicity, No. (%)	
Non-Hispanic white	47 (11.9)
Non-Hispanic black	122 (31.4)
Hispanic	215 (55.4)
Other	5 (1.3)

Abbreviation: *APOE* E4,* apolipoprotein ε4.

Table 2. Prevalence of Each EPS at Baseline, Time of Diagnosis of Dementia, and Last Evaluation

	No. (%)		
	Baseline Evaluation	Time of Incident Dementia	Last Evaluation
EPS dichotomous total score	48 (12.3)	72 (18.5)	88 (22.6)
Speech/facial expression	9 (2.3)	20 (5.1)	32 (8.2)
Tremor at rest	5 (1.3)	7 (1.8)	6 (1.5)
Rigidity	12 (3.1)	20 (5.1)	41 (10.5)
Posture/gait	27 (6.9)	42 (10.8)	53 (13.6)
Bradykinesia	9 (2.3)	23 (5.9)	29 (7.5)

Abbreviation: EPS, extrapyramidal sign.

RESULTS

CHARACTERISTICS OF THE SAMPLE

Three hundred eighty-eight patients with incident AD were included in the study. Basic demographic and clinical characteristics are presented in **Table 1**. Patients were followed up for a mean (SD) of 3.6 (2.6) years, with total follow-up times (from diagnosis to final visit or death) ranging from 0.7 to 13.1 years and an average of 4.1 visits/assessments per patient.

EPS DESCRIPTIVE STATISTICS

Prevalence of any EPS at baseline, time of incidence, and final evaluation are presented in **Table 2**. An increase was observed across time in the frequency of all EPS domains with the exception of resting tremor, which was also less frequent. Similar frequencies were observed across EPS domains (2.3% to 6.9% at baseline, 5.1% to 10.8% at the time of incidence, and 7.5% to 13.6% at the final evaluation).

EPSs OVER TIME

With regard to changes across time, the generalized estimating equation models indicate an increase in all EPSs

Table 3. Changes in EPS Score Across Time (GEE Model)[a]

	Change From Baseline		Change From Time to Incidence	
	β	*P* Value	β	*P* Value
Speech/facial expression	0.068	<.001	0.073	<.001
Rigidity	0.192	<.001	0.270	<.001
Bradykinesia	0.0690	<.001	0.079	<.001
Posture/gait	0.103	<.001	0.122	<.001
Tremor	0.006	.09[b]	0.006	.08[b]

Abbreviations: EPS, extrapyramidal sign; GEE, generalized estimating equation.
[a] All covariates: age, sex, education, ethnicity, and apolipoprotein E.
[b] Not significant.

(continuous score) from both baseline and the time of incidence. The rate of change was an increase of 0.4 and 0.6, respectively, in total EPS score per year of follow-up. The results for each domain are presented in **Table 3**. Only tremor did not significantly increase over time from baseline or from the time of incidence.

Another way to present these results is to calculate the annual increase in EPS total and domain scores. From the time of incident dementia, the annual increase in scores was 1.30% for EPS total, 0.91% for speech/facial expression, 1.35% for rigidity, 1.97% for bradykinesia, 1.52% for posture/gait, and only 0.15% for tremor (**Figure**).

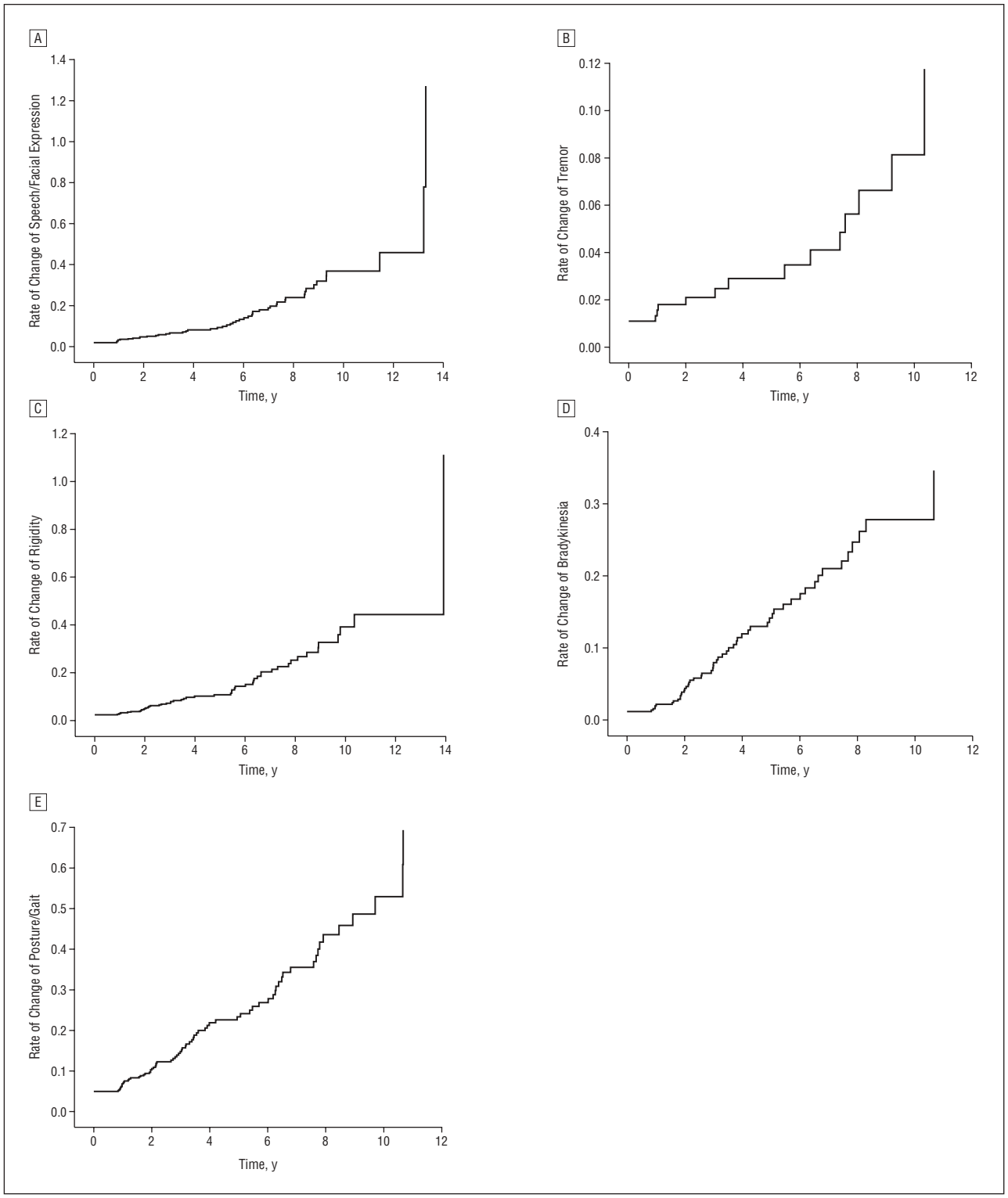

Figure. Cumulative risk (1 – cumulative survival) curves of developing any extrapyramidal sign and individual domain extrapyramidal sign (y-axes). The time axes show the time from the first evaluation until the development of motor signs (or last evaluation). A, Speech/facial expression. B, Tremor. C, Rigidity. D, Bradykinesia. E, Posture/gait.

Table 4. Cox Models Predicting Occurrence of Individual EPSs and Any EPS Overall

	Variable, Risk Ratio (95% CI)			
	Female Sex	Age	Education	Composite Cognitive Score
Speech/facial expression	0.80 (0.43-1.51)	1.01 (0.97-1.05)	1.04 (0.92-1.12)	0.57[a] (0.34-0.96)
Tremor	1.42 (0.52-3.83)	1.05 (0.97-1.12)	0.96 (0.84-1.09)	0.95 (0.36-2.47)
Rigidity	0.88 (0.48-1.59)	1.04[a] (1.01-1.08)	1.10[a] (1.03-1.18)	0.37[a] (0.23-0.59)
Posture/gait	0.65 (0.39-1.08)	1.06[a] (1.03-1.09)	1.07[a] (1.01-1.13)	0.64[a] (0.44-0.94)
Bradykinesia	0.57 (0.30-1.09)	1.05[a] (1.01-1.09)	1.07 (0.40-1.05)	0.65 (0.40-1.05)
Any EPS	0.82 (0.56-1.19)	1.05[a] (1.03-1.08)	1.05[a] (1.01-1.10)	0.58[a] (0.43-0.78)

Abbreviations: CI, confidence interval; EPS, extrapyramidal sign.
[a]Significant association (95% CI not including 1).

Table 5. Cognition Over Time and the Effect of EPS on Cognition (GEE Model)

	Baseline Model		Time of Incidence Model	
	β	*P* Value	β	*P* Value
		Continuous Score		
EPS total score	−0.055	<.001[a]	0.003	.73
Speech/facial expression	−0.171	.003[a]	−0.065	.09
Rigidity	−0.115	<.001[a]	−0.008	.20
Bradykinesia	−0.003	.89	0.018	.58
Posture/gait	−0.103	.01[a]	0.109	.26
Tremor	−0.138	.01[a]	0.113	.86
		Dichotomous Score		
EPS total score	−0.224	.01[a]	−0.165	.06[a]
Speech/facial expression	−0.376	.11	−0.342	.02[a]
Rigidity	−0.407	<.001[a]	0.531	.03[a]
Bradykinesia	−0.124	.55	−0.342	.08
Posture/gait	−0.114	.33	0.109	.26
Tremor	−0.300	<.001[a]	0.016	.93

Abbreviations: EPS, extrapyramidal sign; GEE, generalized estimating equation.
[a]Significant ($P < .05$) coefficients for interaction terms.

The incidence and risk factors for EPS were explored with a Cox model (**Table 4**). Patients with a higher cognitive score at baseline were less likely to develop EPSs (any EPS and 3 domains, including speech/facial expression, rigidity, and posture/gait). Older patients were most likely to develop EPSs (any EPS and 3 domains, such as rigidity, posture/gait, and bradykinesia). Patients with a higher education level were most likely to develop EPSs (any EPS and 2 domains, such as rigidity and posture/gait). Of note, there was no influence of sex and ethnicity.

COGNITION OVER TIME AND THE EFFECT OF EPSs ON COGNITION

We assessed the effect of EPSs on cognition (composite cognitive score) with the generalized estimating equation model (**Table 5**). The presence of EPSs was associated with a lower composite cognitive score (baseline model, β=−0.224, *P*=.01; incidence model, β=−0.165, *P*=.06). Moreover, in the baseline model, patients with tremor (β=−0.300, *P*<.001) and rigidity (β=−0.407, *P*<.001) had lower composite cognitive scores, whereas in the time of incidence model, impaired speech/facial expression was associated with lower composite cognitive scores (β=−0.342, *P*=.02). There was no significant interaction with time, which indicates that the presence of EPSs does not affect rates of cognitive decline over time.

The cognitive decline was explored with Cox models. There were significant effects of sex (relative risk [RR], 1.57; *P*=.03), age at baseline (RR, 1.03; *P*=.02), education (RR, 0.90; *P*<.001), and baseline EPS score (RR, 2.07; *P*=.001).

Patients were thus observed to be more likely to develop cognitive decline if they were female, were older at baseline, or presented some EPS at baseline. Patients with a higher level of education were less likely to develop cognitive decline.

COMMENT

This large community-based prospective study has permitted the observation of the emergence of EPSs in incident AD cases. We found EPSs to be present even in very early stages of AD, sometimes before confirmation of the diagnosis, with their prevalence increasing over time. Compared with other forms of EPS, resting tremor was less frequent and did not increase over time. This observation has also been made by previous stud-

ies.[1,2,8,11,20] Symptoms of EPSs other than resting tremor were seen to progress rapidly over time as previously noted,[1,2,10,11,20] with an annual increase in EPS scores of 0.91% to 1.97%, with only 0.15% for tremor. These calculated rates are smaller or quite close to previously reported ones.[10,11] However, differences with regard to population sampling and baseline levels of EPSs limit direct comparisons.

Extrapyramidal signs and AD may share similar pathogenesis. The presence of one increases the probability of having the other.[3,21] Whether EPSs represent the presence of AD abnormalities, Lewy body disease, or vascular disorders is still uncertain. Explanations other than Lewy bodies for the existence of EPSs in AD include the presence of senile plaques in the putamen, caudate, and substantia nigra; the presence of neurofibrillary tangles in the substantia nigra; and a neuronal loss.[22,23] A main limitation of our study is that the findings are based on a clinical diagnosis of probable AD, without neuropathologic examination.

It is important to note that EPSs may predate the clinical diagnosis of dementia, as observed in previous studies. Mild parkinsonian symptoms have been described in individuals with mild cognitive impairment.[21,24] In a French general population study,[25] 30% of an elderly cohort free of dementia were seen to have at least 1 EPS. Their clinical significance remains unclear. Decline in nigrostriatal dopaminergic regulation with advancing age is probably implicated[26]; however, the observed relationship between EPSs and disability appears to be independent of age, which suggests that EPSs are not a benign feature of a normal aging process.[24] They could be associated with early cognitive symptoms in the course of probable AD and have also been linked to depression, possibly through common effects of underlying dopaminergic changes.

In our study, EPSs occurred in AD in the absence of psychotropic medications, particularly neuroleptics. Wilson and MacLennan[27] found no difference between idiopathic and iatrogenic EPSs except for a higher number of gait EPSs. With regard to difficulties in separation of the relative contribution of neuroleptic use and AD-related sensitivity to neuroleptics, we analyzed non–drug-induced EPSs to increase our confidence that the occurrence of EPSs is strictly related to an underlying disease process.

Baseline EPS symptoms were associated with lower baseline cognitive performance, which suggests either an early impact of the underlying neurologic changes related to EPSs on cognition or that persons with higher performance have increased resistance to EPSs owing to a greater number of synaptic connections that permit longer resistance to clinical manifestations of dopaminergic or serotoninergic loss.

Moreover, studies that concern the cognitive reserve hypothesis suggest that there are individual differences in the ability to compensate for AD lesions.[28-31] Individuals with more cognitive reserve may have AD abnormalities for a longer period before or without clinical expression.[31,32] When AD changes are clinically expressed, the disease is already quite advanced and more severe. Our results are consistent with this hypothesis with regard to EPSs and the level of education. Individuals with higher educational attainment have a higher cognitive reserve.[28,30,31] In this study, patients with a higher level of education were most likely to develop EPSs, which may be a hallmark of more severe disease. Furthermore, in accordance with the previous studies, our study enables us to validate a link between the risk of cognitive decline and a more advanced age at the time of inclusion, a lower sociocultural level, and the presence of EPSs at the time of inclusion.

This study is one of the largest prospective studies on a multiethnic cohort; it allows a detailed and longitudinal analysis of the correlation between EPSs and cognitive decline in AD. The number of incident cases led to analyses with good statistical power and allowed us to examine many covariates. The AD diagnosis was based on a complete analysis of the clinical and neuropsychological data, and the final validation of AD cases was conducted by a multidisciplinary expert team. The EPS evaluation could be limited, because it was a subjective assessment of the various symptoms but was based on a short assessment scale validated in other cohort studies. Finally, the present study confirms the association between EPSs and early AD.

Accepted for Publication: April 30, 2009.
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Financial Disclosure: None reported.
Funding/Support: This work was supported in part by grants P01-AG07232 and RR00645 from the National Institute on Aging and grant 5T32NS007153-22 from the National Institute of Neurological Disorders and Stroke.
Role of the Sponsor: The funding bodies had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

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