

Cumulative Risks of Developing Extrapyrarnidal Signs, Psychosis, or Myoclonus in the Course of Alzheimer's Disease

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• **Cumulative risks of developing extrapyramidal signs, psychosis, and myoclonus in the course of Alzheimer's disease (AD) were estimated in 72 patients with probable AD by the Kaplan-Meier survival method. The cumulative risk functions were found to increase at different rates for different signs as AD progressed. Comparisons of the cumulative risk functions revealed that in the early stages of AD, extrapyramidal signs and psychosis were more likely to develop than myoclonus. As AD progressed, the risk of developing myoclonus became as great as that of developing the other two signs. This study suggests that extrapyramidal signs, psychosis, and myoclonus represent developmental features that mark the progression of AD, rather than indicators of disease subtypes. The estimated cumulative risk functions set a reasonable expectation for the timing and likelihood of the emergence of the clinical signs. This, in turn, might aid in disease prognosis because the biological bases of these signs have been established and they have been shown to be predictive of other markers of disease course.**

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A portion of patients diagnosed with probable Alzheimer's disease (pAD) develop extrapyramidal signs, psychosis, or myoclonus during the disease.¹⁻⁷ These signs have previously been shown to be good predictors of disease progression: patients developing one of the signs by their first clinical evaluation tend to deteriorate to specific cognitive and functional end points sooner than those without these signs.^{8,9} The same patients also have a higher risk of mortality.¹⁰ However, these signs are no more predictors than outcomes by their nature, and knowing that myoclonus predicts faster cognitive decline or death still begs the question of how likely it is that a patient will develop myoclonus at any particular point in disease progression. This study attempted to address this question as well as to determine if different signs tend to emerge at different points in the disease course.

We define risk, throughout the article, as the probability that a patient develops a clinical sign before time t . This is commonly known as the cumulative distribution function ($F(t)$), or simply the cumulative risk, and can be estimated by the Kaplan-Meier survival method.¹¹

SUBJECTS AND METHODS

Subjects

Seventy-two patients (34 men, 38 women) met the *Diagnostic and Statistical Manual of Mental Disorders-III-Revised* criteria for primary degenerative dementia¹² and the National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for probable AD.¹³ This is the same cohort of patients that was used in previous studies of the predictive value of clinical signs,^{1,8-10} and consisted of a consecutive series of patients presenting for evaluation of dementia in a clinical practice. Inclusion in the study was not dependent on disease severity or the presence or absence of symptoms.

Mean age at onset of the disease was 64.11 (SD = 9.39) years. Mean duration of illness by first clinical evaluation was 2.95 (SD = 1.63) years.

Patients were followed up for an average of 5.05 years (SD = 2.29) and evaluated at least twice, with a minimum interval of 6 months between evaluations. Twenty-nine patients were followed up to death; autopsy was obtained in eight patients and AD was confirmed in all.

Procedures

All neurologic and psychiatric evaluations were conducted by the same investigator (R.M.).

Extrapyramidal Signs and Myoclonus.—Extrapyramidal signs (EPSs), including tremor, rigidity, bradykinesia, gait, postural change, and masked faces, were rated using selected items from the Unified Parkinson's Disease Evaluation.¹⁴ A patient was considered to have EPS if any rated sign was present. All medications were recorded.

If a patient took any medication that might have caused EPS, the occurrence of these signs was not counted in the analyses. This conservative approach limits statistical power to some degree but ensures that only true EPSs are evaluated.

Myoclonus was rated as absent, present with sleep only, present with startle only, or present while awake or asleep.

Psychosis.—All patients and available family members or informants were interviewed in a semistructured fashion to assess the presence of psychiatric symptoms, using the *Diagnostic and Statistical Manual of Mental Disorders-III-Revised* as a guideline. The presence of persistent hallucinations, illusions, or delusions was sufficient to

rate a patient as having psychosis.

Determining Onset of AD.—At the first visit, the patients and reliable informants were interviewed to determine the date at which the patient first met the criteria for the diagnosis of pAD. The reliability of our onset assessments was confirmed using standardized interview techniques.¹⁵

Determining Onset of a Clinical Sign.—Onset of a clinical sign was estimated as the date when the sign was first noted by a neurologist on one of the patient's visits. Although this estimation tended to bias the actual onset toward a later date, it was assumed that the bias existed to the same extent in estimates of all three clinical signs and, therefore, would only affect the absolute onset dates of the signs but not the comparisons between them.

Analysis

Kaplan-Meier survival analysis^{11,16} was used to estimate the cumulative risks of developing the clinical signs during the disease. The SAS LIFETEST procedure was used in the computing of the cumulative risk functions.¹⁷ Binomial tests were employed to compare the times of occurrence of the signs. In addition, the percentages of patients who evidenced the clinical signs (prevalence) as well as the number of patients who developed them (incidence)¹⁸ were calculated. These values were not meant to estimate the population prevalence and incidence parameters, but to estimate how frequently the signs were noted in this particular sample.

RESULTS

Survival Analyses

Kaplan-Meier survival analysis was employed to estimate the cumulative risk for developing each clinical sign by defining the first occurrence of a sign as the end point. The cumulative risk functions for the three signs over the disease period were then compared. As shown in the Figure, the cumulative risk of developing EPS resembled that of developing psychosis, and both were greater than the cumulative risk of developing myoclonus. As the disease progressed, the risk of developing myoclonus became as great as those of developing EPS and psychosis. Wilcoxon's rank sum test yielded a χ^2 of 7.34, $P = .025$ (The test assumes independence among the cumulative risk functions under comparison, which was not the condition in our study since some patients have developed more than one sign and the three cumulative risk functions were based on overlapping subjects. The test, however, can be used as a conservative one to demonstrate the difference among the cumulative risk

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functions). These results suggested that EPS and psychosis tended to emerge earlier than myoclonus in the course of AD.

Binomial Tests

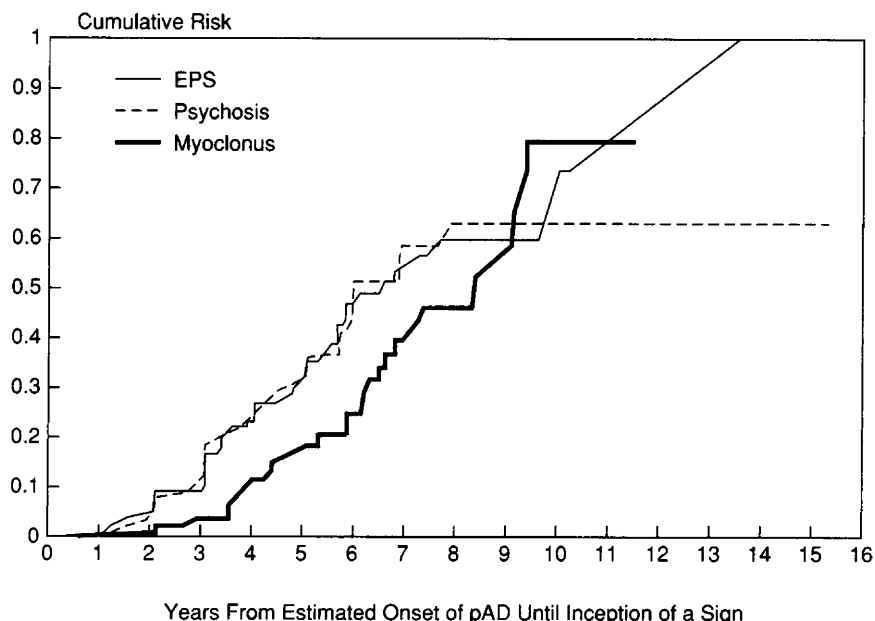
To further support the observation that EPS and psychosis tended to emerge earlier than myoclonus, the number of patients in whom the occurrence of each sign preceded another was examined in two-tailed binomial tests. To prevent an increase of type 1 error rate in multiple tests, Bonferroni correction was applied to yield an adjusted significance level of .017 (.05/3). The EPS occurred before myoclonus in 30 of 43 patients ($z = 2.44$, $P = .015$), psychosis occurred before myoclonus in 30 of 44 patients ($z = 2.26$, $P = .024$), while EPS occurred before psychosis in 22 of 41 patients ($z = 0.38$, $P = .76$). These results are, therefore, consistent with the findings obtained in the survival analyses.

Presence and Occurrence of the Three Clinical Signs

The percentage of patients displaying EPS, psychosis, and myoclonus at the first clinical evaluation (prevalence) was 27.8%, 25%, and 6.9%, respectively. Overall, the percentage of patients displaying clinical signs by the last clinical visit were 51%, 47%, and 39% for EPS, psychosis, and myoclonus, respectively. The percentage of patients without a clinical sign at the first evaluation who developed one during follow-up (incidence) was 32.7% for EPS, 29.7% for psychosis, and 34.3% for myoclonus. Because patients were followed up for different lengths of time, we took the total number of new cases during the follow-up period and divided it by the sum of follow-up time for all patients being followed up. The result was multiplied by 1000 and expressed as cases per 1000-person years. The incidence rates from the first to the last evaluation are 101, 102, and 115 cases per 1000-person years for EPS, psychosis, and myoclonus, respectively (Table).

COMMENT

In this study, we have taken a different perspective on EPS, psychosis, and myoclonus, viewing them as disease outcomes rather than predictors. We found that the cumulative risks of developing EPS, psychosis, and myoclonus are different during the course of pAD. It appears that a patient with pAD is more likely to develop EPS or psychosis than myoclonus during the first few years of the disease. As disease pro-



Cumulative risks of developing extrapyramidal signs (EPS), psychosis, or myoclonus in the course of probable Alzheimer's disease (pAD), estimated from the Kaplan-Meier survival analysis.

Prevalence by First Clinical Evaluation, Incidence, and Incidence Rate (Cases per 1000-Person Years) During Follow-up Period, and Prevalence by Last Clinical Evaluation for EPs, Psychosis, and Myoclonus*				
	Prevalence at First Clinical Evaluation %	Incidence During Follow-up Period, %	Incidence Rate During Follow-up Period (per 1000 person years)	Prevalence at Last Clinical Evaluation, %
EPs	27.78	32.69	101	51.39
Psychosis	25.00	29.63	102	47.22
Myoclonus	6.94	34.33	115	38.89

*EPs indicates extrapyramidal signs.

*Values are intended to be descriptive of the study group only, not of the general population.

gresses, myoclonus becomes as likely to occur as the other signs. The estimated cumulative risk functions provide a reasonable expectation of how likely it is for a clinical sign to emerge at any point in the disease. This, combined with the demonstrated predictive value of the signs, should help in planning care and treatment of patients.

We observed a frequency of 6.9% for myoclonus by the first clinical evaluation, which is similar to 6.2% reported by Chui et al⁸ their cross-sectional study. In addition, we found that myoclonus has a high incidence rate but a low prevalence rate. This suggests that myoclonus is not rare in pAD; perhaps because the duration of pAD is decreased after its appearance,¹⁰ prevalence is low. This is not true for EPS and psychosis, however. In fact, when the incidence rates are compared, it is myoclonus that seems to have a higher frequency of occurrence than the other two clinical signs.

There are some caveats to the interpretation of the results. First, in determining the onset of clinical signs, we made an assumption that a sign is nonreversible once it emerges. Although clinicians generally agree that EPS is not reversible, subtle EPS may be noted on one visit but not on a following visit, or vice versa, which makes the onset estimate somewhat problematic. An ideal way of resolving this problem is to examine a patient's EPS ratings on successive visits and determine when the sign was consistently noted on two or more consecutive visits. Unfortunately, our data do not contain enough follow-ups to allow for such a clarification. Psychosis faces even a greater difficulty, since the nonreversibility assumption is usually not justified. On the other hand, myoclonus seems to enjoy greater certainty in its detection and nonreversibility can be more safely assumed. A related set of issues that cannot be addressed with these data is whether, in patients with

one EPS, others tend to develop in time. Similarly, the relative importance of each EPS in our incidence figures is not evaluated due to restricted power.

Second, it may be argued that our sample has included unusual cases and was biased. However, our sample does not seem to be more biased than other similar studies because the prevalences of the three signs as we observed are not higher than those observed by others.^{3,5,19-21} It is possible, of course that the referral patterns of patients to our center differ from those to other centers in some systematic way. For this reason, confirmatory studies across centers would help to confirm the natural history of the clinical signs as presented here.

Extrapyramidal signs must be distinguished from unrelated manifestations of AD. For example, a patient may be apathetic, but facial immobility will be apparent even when his interest is engaged. A patient may take uncertain steps because of confusion over his/her destination, but this cannot be confused with the shuffling gait observed while the patient is walking several feet to a certain destination. Similarly, paucity of movement unrelated to EPS must be distinguished from bradykinesia during elicited movements. These distinctions require clinical judgment. In this study, reliability of these ratings is ensured by the use of only a single rater.

The results imply that EPS, psychosis, and myoclonus are developmental markers of AD that every patient will eventually develop if they live long enough. This view is not consistent with the concept that these signs define subtypes of pAD.^{1,2,3,6,7,22} According to the subtype concept, patients developing myoclonus in the course of AD form a distinct group, which differs pathologically, and perhaps etiologically as well, from the group who develop EPS or other clinical signs. The concept implies mutual exclusiveness of the subtypes. It also suggests that some patients will develop myoclonus, for example, while others will not. Our data show that some patients developed more than one clinical sign during the disease, eg, myoclonus as well as EPS. They also suggest that it is probable that every patient will eventually develop myoclonus, but with the risk differing during the course of disease.

We suggest that it might be more appropriate to view the various clinical signs, be they EPS, psychosis, myoclonus, specific levels of functional or cognitive deterioration, or even death, as different disease markers or outcomes that emerge at different stages of the disease. Given that individuals are

born with somewhat different biological makeups, it is reasonable to tolerate a certain degree of variability as to when each sign will emerge in an individual patient. In other words, clinical heterogeneity need not be interpreted as indication of disease subtypes; rather, it may be explained as reflecting variation in a probability distribution whose parameters are estimable. An advantage of this view is that each disease feature is allowed to emerge with different probabilities at different times, and its relationship with other disease features can be properly assessed. For example, some disease features may have a higher probability of occurring earlier than others. Knowledge of this can help determine the temporal order of occurrences of the various disease features in the course of AD. In addition, one can examine how the occurrence of one disease feature affects, or is affected by, the occurrence of another disease feature. Our previous work⁸⁻¹⁰ on the three clinical signs as predictors of cognitive and functional deterioration as well as mortality constitutes an attempt along this line. Our article provides a broader view of the issue in the sense that the clinical signs, when looked on as developmental markers, can serve as outcomes just as well as serving as predictors.

It is important to note that the probabilistic view adopted here does not strictly rule out the concept of subtypes. For instance, it is conceivable that a certain group of patients, for example those with a family history of AD, may have a higher risk of developing a particular disease feature than another group.^{23,24} In other words, there can be different disease courses for different disease subtypes, with each course being described in the same probabilistic manner. On the other hand, the identification of a subtype should be evaluated against a probabilistic view so that a subtype is not merely reflecting sample heterogeneity or natural individual differences.

As the temporal probability distributions of sufficient disease outcomes are determined and the relationship among them examined, a more complete picture of the natural history of AD may start to emerge. It may, then, become conceivable to predict the course of an individual's disease based on the presence or absence of any of these signs.

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