Original Paper

European Neurology

Eur Neurol 1996;36:103–106

Clinical Features and Mortality in Patients with Early-Onset Alzheimer's Disease

William N. Samson
Cornelia M. van Duijn
Wim C.J. Hop
Albert Hofman

Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, The Netherlands

Key Words
Alzheimer's disease
Prognosis
Epidemiology

Abstract
In a population-based study of 198 patients with probable early-onset Alzheimer's disease (AD), we studied the occurrence of extrapyramidal signs (tremors and rigidity), myoclonus, psychosis and seizures, as well as their predictive value for mortality. The presence of tremors was significantly associated with the presence of rigidity. The occurrence of myoclonus was significantly associated with the occurrence of seizures. Psychosis and seizures in AD patients were not associated with mortality. The occurrence of extrapyramidal signs and myoclonus at any point in time during the course of AD increased the risk of mortality significantly. When evaluating their relative importance, extrapyramidal signs appeared to be the most important predictor of mortality.

Introduction

Alzheimer's disease (AD) is often accompanied by the development of extrapyramidal signs [1], myoclonus [1–3], psychosis [1], seizures [2, 3], and aphasia [4]. Several studies have shown that patients developing these signs deteriorate more rapidly [4–7]. Few studies have examined how the occurrence of concomitant clinical features in AD relates to mortality. One study has suggested that mortality may be related to extrapyramidal signs and myoclonus [8], while another study has suggested that aphasia is associated with an increased risk of death [9]. In this paper we report the results of a study of the occurrence of extrapyramidal signs, myoclonus, psychosis and seizures in patients with early-onset AD. The study focused on the relationship between these clinical features and their prognostic value for mortality in patients with early-onset AD.

Patients and Methods

Patients were derived from a population-based case-control study of early-onset AD [10]. The ascertainment of the patients has been described earlier [10]. All patients met the criteria for probable AD [11]. Mean age at first symptoms was 57 years for men (range 34–64) as well as women (range 40–64). Mean age at diagnosis of AD was 61 years (men: range 37–70; women: range 47–69). Data on medication and the occurrence of clinical features were collected upon inclusion in the study (1980–1987), through medical records from the general hospital where the patient was diagnosed and from the nursing home.

KARGER
E-Mail karger@karger.ch
Fax + 41 61 306 12 34

0014–3022/96/0362–0103$10.00/0

Dr. C.M. van Duijn
Department of Epidemiology and Biostatistics
Erasmus University Medical School
PO Box 1738
NL–3000 DR Rotterdam (The Netherlands)

Received:
November 17, 1994
Accepted:
July 28, 1995

Table 1. Clinical features in patients with early-onset AD at different times

	Presence ever during AD (n = 190)	Presence at diagnosis (n = 190)	Presence at nursing home admission (n = 177)
Tremor	37 (20)	9 (5)	17 (10)
Rigidity	69 (36)	10 (5)	14 (8)
Tremor or rigidity	83 (44)	15 (8)	25 (14)
Myoclonus	68 (36)	4 (2)	13 (7)
Psychosis	69 (36)	18 (10)	23 (13)
Seizures	94 (45)	13 (7)	19 (11)

Figures in parentheses are percentages.

In the Netherlands, patients are examined upon admission to a nursing home, and concomitant features as well as medication at admission and thereafter are recorded. Extrapyramidal signs were assessed by the occurrence of tremors and rigidity, psychosis by the occurrence of delusions and hallucinations. We considered only clinical features that were not related to medication. In 1990, the medical records from the general hospital and nursing home were updated and vital status was assessed for all patients. The mean period of patient follow-up after diagnosis was 6 years (range 2–15). Of the 198 patients, 190 (96%) could be traced and 177 (93%) had been admitted to a nursing home. Mean age at admission was 63 years (men: range 39–71; women: range 54–71).

Data Analysis

Odds ratios with 95% confidence interval (CI) were used to study the relationship between clinical features [12]. Kaplan-Meier survival curves [13] and log rank tests [14] were used to estimate and compare survival. For each feature, the age- and sex-adjusted death rate ratio (DRR) was estimated using Cox regression [15]. All analyses were adjusted for the fact that not all patients were included in our study at the same time (left truncation) [16]. Time-dependent covariate modelling was used to investigate the influence of features on prognosis at different points in time [17].

Results

In table 1, the occurrence of clinical features is presented. The presence of tremors was associated with a risk of rigidity increased 7.2 times (95% CI: 2.7–19.4; p = 0.001) (not in table). The risk of seizures for patients with myoclonus was increased 7.7 times (CI: 2.6–22.8; p = 0.001) compared to the risk for patients without myoclonus. Nine out of 16 patients with myoclonus (56%) had a history of seizures.

The association between mortality and the presence of clinical features is presented in table 2. The presence of tremors, rigidity and myoclonus at diagnosis and nursing home admission significantly predicted lower survival rates. The median survival time from diagnosis onwards for patients with tremors was 2.5 years, for those with rigidity 3.0 years and for those with myoclonus 2.8 years, as compared to 6 years for patients without these clinical features. None of the associations were modified by age or gender, and estimates did not change when adjusting for the severity of dementia at diagnosis using the score on the Clinical Dementia Rating Scale [18].

In the time-dependent model (table 3), extrapyramidal signs (DRR 2.9; CI 1.8–4.5; p = 0.001) and myoclonus (DRR 2.4; CI 1.5–3.9; p = 0.001) at diagnosis or thereafter were associated with worse survival. In order to adjust for the correlation between various clinical features, all features were included in a model, and relevant predictors for survival were chosen by backward selection. In this analysis, extrapyramidal signs were found to be the most important predictor of survival (DRR 1.9; CI 1.1–3.1; p = 0.01).

Discussion

In this population-based study of early-onset AD, the occurrence of extrapyramidal signs and myoclonus was associated with a statistically significantly increased risk of mortality. Extrapyramidal signs appeared to be the most important predictor of survival. Regarding the validity, the occurrence of extrapyramidal signs, myoclonus, psychosis and seizures was assessed through medical records. Consequently, diagnosis of the clinical features was not fully standardized, and clinical criteria for the diagnosis of concomitant features may differ between clinicians with different specialties. However, such misclassification is expected to be independent of survival and although it may have diminished associations, it is unlikely that it has created a relationship between a clinical feature and mortality. The fact that our findings on the prevalence of extrapyramidal signs, myoclonus, and psychosis agree with those of a 5-year follow-up study [1] suggests that the effect of misdiagnosis may have been limited. An important advantage of our study is the population-based design including all institutionalized and noninstitutionalized patients in the areas studied.

Our study shows that the presence of myoclonus was associated with seizures, suggesting a shared cortical pathology underlying these features in early-onset AD [3,

Table 2. Survival in patients with early-onset AD after diagnosis and nursing home admission

		Survival after diagnosis				Survival after nursing home admission			
		at 5 years %	median years	DRR[1]	p	at 5 years %	median years	DRR[2]	p
Tremor	+	25	2.5	2.4	0.03	29	2.6	1.9	0.03
	−	61	6.1	(1.1–5.5)		45	4.4	(1.1–3.2)	
Rigidity	+	27	3.0	2.4	0.04	25	3.0	2.0	0.03
	−	62	6.3	(1.0–5.8)		47	4.4	(1.1–3.6)	
Tremor or rigidity	+	28	2.8	2.5	0.01	29	2.7	1.9	0.01
	−	65	6.3	(1.3–4.8)		48	4.8	(1.1–3.1)	
Myoclonus	+	13	2.8	2.9	0.04	14	2.5	1.9	0.05
	−	64	6.3	(1.0–7.9)		48	4.5	(1.0–3.7)	
Psychosis	+	54	5.2	0.9	0.84	46	5.0	0.8	0.49
	−	62	6.1	(0.4–2.2)		42	4.3	(0.5–1.5)	
Seizure	+	56	6.1	0.7	0.55	43	4.3	0.6	0.15
	−	63	6.1	(0.3–2.0)		42	4.3	(0.3–1.2)	

[1] Adjusted for age and gender; 95% CI in parentheses.
[2] Adjusted for age, gender, and time between diagnosis and nursing home admission; 95% CI in parentheses.

19]. However, myoclonus may not be distinguished from epilepsy by nursing-home physicians as repeated EEG recordings may be needed. Therefore, our findings on the clustering of seizures and myoclonus remain to be confirmed.

Our study indicates that mortality of the subgroup of patients with an early-onset of AD is associated to extrapyramidal signs and myoclonus. A number of studies have suggested that patients with these features may progress more rapidly [1–3, 6, 11, 20]. However, only one study has reported that their presence increased the risk of mortality [8]. Our findings and those of others [8] suggest that despite the relationship of psychosis [5, 6] and seizures [2, 3] to cognitive decline, these features are not related to mortality.

When evaluating the relative importance of predictors, extrapyramidal signs appeared to be the most important predictor of mortality in patients with early-onset AD in our study. In the absence of pathological confirmation, however, it remains to be determined whether a number of our patients with clinical AD actually suffer from Lewy body disease and have thus been misdiagnosed.

Table 3. Clinical features and survival of patients with early-onset AD (time-dependent model)

	DRR[1]	95% CI	p
Tremor	1.6	0.9–2.7	0.08
Rigidity	2.6	1.7–4.1	<0.001
Tremor or rigidity	2.9	1.8–4.5	<0.001
Myoclonus	2.4	1.5–3.9	<0.001
Psychosis	1.2	0.8–2.0	0.39
Seizures	1.3	0.8–2.1	0.24

[1] Adjusted for date of birth, gender and age at diagnosis.

Acknowledgments

This study was supported by the Steering Committee for Research on Ageing, The Netherlands Organisation for Scientific Research (NWO) and the Netherlands Institute for Health Sciences (NIHES). The authors are grateful to Drs. Wim Schulte, Teun Tanja, Rob Haaxma, Arie Lameris and Rolf Saan for their contributions to patient diagnosis and Helen de Bruijn, Micheline de Haes, Jeanette Kamman, Irene van Koppen, Hilda Kornman, Hanneke van Meurs and Caroline Valkenburg for data collection.

References

1 Chen JY, Stern Y, Sano M, Mayeux R: Cumulative risks of developing extrapyramidal signs, psychosis, or myoclonus in the course of Alzheimer's disease. Arch Neurol 1991;48:1141–1143.

2 Risse SC, Lampe TH, Bird TD: Myoclonus, seizures, and paratonia in Alzheimer disease. Alzheimer Dis Assoc Disord 1990;4:217–225.

3 Hauser WA, Morris ML, Heston LL, Anderson VE: Seizures and myoclonus in patients with Alzheimer's disease. Neurology 1986;36:1226–1230.

4 Faber-Langendoen K, Morris JC, Knesevich JW: Aphasia in senile dementia of the Alzheimer type. Ann Neurol 1988;23:365–370.

5 Stern Y, Mayeux R, Sano M: Predictors of disease course in patients with probable Alzheimer's disease. Neurology 1987;37:1649–1653.

6 Stern Y, Hesdorffer D, Sano M, Mayeux R: Measurement and prediction of functional capacity in Alzheimer's disease. Neurology 1990; 40:8–14.

7 Knesevich JW, Toro FR, Morris JC, LaBarge E: Aphasia, family history, and the longitudinal course of senile dementia of the Alzheimer type. Psychiatry Res 1985;14:255–263.

8 Stern Y, Mayeux R, Chen JY, Sano M: Predictors of mortality in Alzheimer disease. Ann Neurol 1989;26:132.

9 O'Carroll R, Whittick J, Baikie E: Patients' signs and sinister prognosis in dementia. A four-year follow-up study. Br J Psychiatry 1991;158:358–361.

10 van Duijn CM, Hofman A: Relation between nicotine intake and Alzheimer's disease. BMJ 1991;302:1491–1494.

11 McKhann G, Drachman D, Folstein M: Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.

12 Breslow NE, Day NE: Statistical methods in cancer research. Lyon, International Agency for Research on Cancer (IARC) Scientific Publications, 1980, No 32.

13 Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.

14 Elandt-Johnson RC, Johnson NL: Comparison of mortality experiences. Survival models and data analysis. New York, Wiley, 1980, pp 258–260.

15 Cox DR: Regression models and life tables. JR Stat Soc 1972;34:187–220.

16 Kurtzke JF: On estimation survival: A tale of two censors. J Clin Epidemiol 1989;42:169–175.

17 Hop WCJ, Van Buuren HR: A method to evaluate changes in prognostic status during follow-up, illustrated by an assessment of the effect of a rebleed in patients with oesophageal variceal bleeding. Comput Biol Med 1989;19:181–188.

18 Hughes CP, Berg L, Danziger WL: A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–572.

19 Wilkens DE, Hammett M, Berardelli A, Walshe T, Alvarez N: Physiological analysis of the myoclonus of Alzheimer's disease. Neurology 1984;34:898–903.

20 Morris JC, Drazner M, Fulling K, Grant EA, Goldring J: Clinical and pathological aspects of parkinsonism in Alzheimer's disease. A role for extranigral factors? Arch Neurol 1989;46:651–657.