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BRIEF COMMUNICATION

A simple test of copying ability and sex define survival in patients with early Alzheimer's disease

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ABSTRACT

Background. We studied whether heterogeneous profiles of cognitive function are relevant to survival in patients with early Alzheimer's disease.

Methods. CAMCOG subscales of cognitive function were used as predictors of survival, together with gender in 157 consecutively referred patients with early Alzheimer's disease. Statistical analysis was performed with Cox proportional hazards analysis and Kaplan–Meier survival curves. Survival rates were compared with those in the general population.

Results. Eighty patients (51%) died during the follow-up that extended to 5·7 years, with a median survival of 4·4 years after entry. Only the praxis subscore was statistically significant related to survival ($P < 0{\cdot}0001$). Its predictive power was based on only two items, including copying ability for a spiral and a three-dimensional house, independent of age, sex, education, overall CAMCOG score, dementia severity and symptom duration. Kaplan–Meier curves for the combined score of these items (0, 1, or 2) showed three groups with significantly different survival rates for both men and women. Comparison of gender specific survival rates with data from the general population showed that excess mortality was statistically significant ($P < 0{\cdot}01$) higher in men (51%) than in women (21%) after follow-up extending to 5 years.

Conclusions. A simple test of copying ability defines subgroups of AD patients with large differences in survival rates. This suggests that parietal lobe impairment is an important predictor of mortality in AD. Also, the course of AD may be more benign in women than in men.

INTRODUCTION

Parietal lobe impairment may define clinically relevant subgroups in Alzheimer's disease (AD) (Blennow & Wallin, 1992). This impairment is reportedly associated with a poor prognosis in AD, but relatively few patients have been studied (Naguib & Levy, 1982) and diagnostic procedures for dementia have not been well-defined (McDonald, 1969). A more recent study found that apraxia was a predictor of mortality in men, but not in women with AD (Moritz *et al*. 1997). Although several reports show that men with AD are at greater risk of death than women with AD (Burns *et al*. 1991; Heyman *et al*. 1996; Claus *et al*. 1998), no attempts have been made to assess excess mortality in relation to general population findings in a cohort of early AD patients with long follow-up. Therefore, we studied the relation between scores of specific items of the CAMCOG neuropsychological test and survival in consecutive patients diagnosed with early AD in relation to age and sex.

METHOD

Subjects

Patients met criteria for probable or possible AD according to NINCDS-ADRDA criteria (McKhann *et al*. 1984) and were participants in

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a prospective study of 200 consecutive first referrals to our out-patient memory clinic (Walstra *et al*. 1997). At baseline, subjects were evaluated with the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX-N) (Roth *et al*. 1988; Derix *et al*. 1991). Of the 200 patients, 163 were diagnosed as having AD (105 probable, 58 possible; 66 men, 97 women) (McKhann *et al*. 1984). Survival data were obtained from general practitioners and were available for all AD patients. CAMCOG data of six patients were incomplete, leaving 157 (64 men, 93 women) for the present analysis. Three patients were treated with oestrogen replacement therapy.

Assessment of cognitive function

Cognitive subscales were used from the CAMCOG, part of the CAMDEX-N (Derix *et al*. 1991), the Mini-Mental State Examination (MMSE) (Folstein *et al*. 1975) is part of the CAMCOG. The CAMCOG sumscore has a high test–retest reliability and includes 60 items divided in eight subscales assessing orientation, language, memory, praxis, attention, abstract thinking, perception, and calculation (Lindeboom *et al*. 1993).

Statistical analysis

Cox regression analysis was used to estimate the effects of baseline variables on survival. Hazard ratios with 95% confidence intervals are presented as estimates of these relationships. Baseline predictors were the subscales of the CAMCOG.

Statistical analysis was performed in several steps. Guided by studies of parietal lobe function in AD in relation to clinical heterogeneity (Blennow & Wallin, 1992) and survival (McDonald, 1969; Naguib & Levy, 1982; Moritz *et al*. 1997), we first assessed the effect of the praxis subscale on survival, adjusted for age and sex. Then, we tested whether the remaining CAMCOG subscales could add prognostic information to the praxis subscale by entering all other CAMCOG subscales as covariates into the Cox regression model. Subsequently, we examined individual items from the praxis subscale and we combined those questions that were independently related to survival into a sumscore. We adjusted this model for diagnosis probable or possible AD, baseline overall CAMCOG score, dementia severity, symptom duration, and education. Survival curves were constructed using the Kaplan–Meier method. Proportionality of the hazard (Collet, 1994) was assessed as we described earlier (Claus *et al*. 1998). We also compared survival rates of AD patients with those of the general population (life tables for the Netherlands) (Verheul *et al*. 1993), using the same age, sex, and calendar period (Hakulinen & Abeywickrama, 1985). We used the cumulative relative survival ratio to assess excess mortality and this was defined as the ratio of the observed survival rate (proportion of patients alive) to the expected survival rate in the general population. Equality of relative survival rates in women and men were tested using the test statistic proposed by Hakulinen & Abeywickrama (1985). Cox regression analysis was used to determine the effects of baseline characteristics on survival that were statistically, significant different among men and women, with the exception of age, since age was used to match persons from the general population in the analysis of excess mortality.

RESULTS

Eighty of 157 patients (51%) died during follow-up. There were several statistically significant differences between men and women by *t* test: mean age (men $77{\cdot}7 \pm 6{\cdot}1$ *v*. women $80{\cdot}1 \pm 6{\cdot}2$, $P < 0{\cdot}05$); education ($3{\cdot}6 \pm 1{\cdot}4$ *v*. $2{\cdot}9 \pm 1{\cdot}5$, $P < 0{\cdot}01$; 7-point scale); symptom duration in months ($42{\cdot}7 \pm 37{\cdot}2$ *v*. $31{\cdot}6 \pm 25{\cdot}1$, $P < 0{\cdot}05$); CAMCOG ($67{\cdot}3 \pm 18{\cdot}5$ *v*. $57{\cdot}0 \pm 14{\cdot}8$, $P < 0{\cdot}01$); and MMSE ($19{\cdot}3 \pm 5{\cdot}9$ *v*. $16{\cdot}9 \pm 4{\cdot}8$, $P < 0{\cdot}01$). Most patients had mild dementia (87%), some were moderately severe demented (13%), and average survival was $40{\cdot}3 \pm 17{\cdot}4$ months.

Lower performance on the praxis subscale was statistically significant related increased mortality (hazard ratio (95% CI): 0·77 (0·70, 0·84), $P < 0{\cdot}0001$). When all CAMCOG subscales were entered into the model, praxis was the only subscale significantly associated with survival, independent of age and sex (hazard ratio (95% CI): 0·82 (0·72, 0·93), $P < 0{\cdot}01$). Analysis of all eight items of the praxis subscale, showed that only the relations between drawing a spiral (hazard ratio (95% CI): 0·56 (0·33,

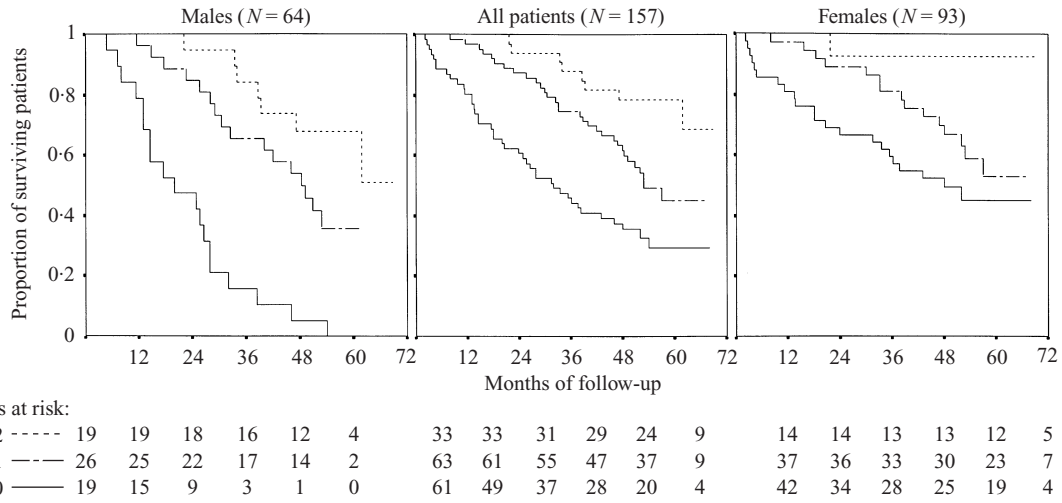

FIG. 1. Copying ability at first time of diagnosis affecting survival in patients with Alzheimer's disease using the Kaplan–Meier method. Three groups were defined according to a sum score of copying a spiral and a three-dimensional house (log rank test: high *versus* intermediate, $P = 0{\cdot}02$; intermediate *versus* low, $P = 0{\cdot}002$; high *versus* low, $P < 0{\cdot}0001$). Curves are shown for men and women separately.

0·96), $P < 0{\cdot}05$) and a three-dimensional house (hazard ratio (95% CI): 0·25 (0·12, 0·55), $P < 0{\cdot}001$) were significantly associated with survival, independent of age, sex, education, total CAMCOG score, and diagnosis probable or possible AD. We combined drawing a spiral (score 0 wrong, or 1 correct) and a three-dimensional house (score 0 or 1) into a new score of copying ability (score 0, 1 or 2), defining three groups at baseline. Kaplan–Meier curves (Fig. 1) showed in the group with a copying ability score of 0 that 28·2% were alive after 66·5 months (median survival 32 months), in the group with score 1 there were 43·5% alive after 65·2 months (median survival 53 months), and in the group with score 2, 65·2% patients were alive after 62·0 months (median survival at least 62·0 months). Log rank tests revealed statistically significant differences between all three groups, for both men and women separately and combined (Fig. 1).

The cumulative relative survival rate was 0·67 for all AD patients after 5 years, indicating an excess mortality of 33% compared with the general population over this period. After 5 years, the relative survival rate was 0·79 (excess mortality 21%) for women ($P < 0{\cdot}01$) and 0·49 (excess mortality 51%) for men ($P < 0{\cdot}0001$), indicating that both women and men with AD have higher mortality than persons in the general

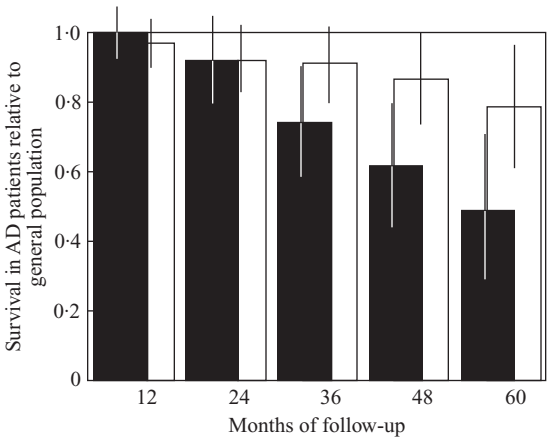

FIG. 2. Cumulative relative survival rates (number of patients alive expressed as percentage from the expected number alive in the general population) for AD patients, significantly different for men (■) and women (□) by regression analysis ($P < 0{\cdot}01$).

population (Fig. 2). The relative survival rates in women and men showed a statistically significant difference ($P < 0{\cdot}01$). Investigation of significantly different baseline characteristics between men and women showed that lower CAMCOG score (hazard ratio (95% CI) per 10 points decrease: 0·78 (0·68, 0·89)) and lower MMSE score (per 5 points decrease: 0·69 (0·57, 0·84)) were related to increased risk of mortality, but

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not education (1·02 (0·88, 1·18)) and symptom duration (per year: 0·92 (0·83, 1·03)).

Linearity and proportionality assumptions of the hazard were met for all variables, except for the hazards for men and women that were not proportional, due to an inverse effect of gender in the first short observation period, resulting in increasing relevance of prognostic value with follow-up time.

DISCUSSION

The praxis subscale of the CAMCOG was strongly associated with survival, independent of age and sex. Combination of only two items testing copying ability defined three groups with statistically different rates of survival. It is important to note that these differences were large and independent of diagnosis probable or possible AD, education, dementia severity, symptom duration, or baseline CAMCOG score. Men showed a statistically significant higher excess mortality than women, in comparison with survival characteristics from the general population, suggesting a more benign course for AD in women than in men.

Impairment of parietal lobe function predicted survival to a certain extent in several small studies of patients diagnosed with senile dementia (McDonald, 1969; Naguib & Levy, 1982). Burns *et al*. (1991) showed that apraxia (from CAMCOG) was associated with early death in AD patients, rather than memory impairment or language disability. Also in agreement with our findings, apraxia was among the cortical functions investigated the strongest predictor of mortality in AD patients (Moritz *et al*. 1997). In this study, however, the relation between apraxia and survival was statistically significant in men but not in women (Moritz *et al*. 1997), contrasting our observations. Their sample was more severely demented than in our study and cortical functions were not examined by neuropsychological assessment. Copying ability, considered as parietal lobe function (Benton & Tranel, 1993), was associated with survival in AD independent of overall severity of disease features and education in our study. This suggests that parietal lobe function defines clinical subgroups of AD patients (Blennow & Wallin, 1992) in relation to survival, regardless of global dementia status. These subgroups may have a neuropathological correlate in the amount of accumulation of senile plaques in parietal association areas (Arriagada *et al*. 1992).

Our finding of different excess mortality in men and women in a sample of early AD outpatients has not been reported before. Consistent with our results, higher relative mortality in men than in women is reported in nursing home patients with dementia (van Dijk *et al*. 1992). No differences between standardized mortality ratios between men and women were found in severely demented AD patients with short follow-up (18·4 months) (Burns *et al*. 1991). Indeed, sex differences in excess mortality in our study became apparent only after 3 years of follow-up. The increased excess mortality in men can not readily be explained by differences in baseline characteristics. In fact, women had significantly lower CAMCOG scores at baseline, associated with increased mortality in the proportional hazard model. Recently it has been suggested that oestrogen use in post-menopausal women may delay the onset and decrease the risk of AD (Tang *et al*. 1996). It is tempting to speculate that our results, which suggest that women with AD show a more benign course than men, are related to pre- or post-menopausal effects of oestrogen.

In spite of the large differences in survival according to parietal lobe function, these may be chance findings and they need to be replicated in a prospective study of a larger patient group, using incident cases of dementia. Possible confounders not examined in our study, such as atherosclerotic vessel disease, should be investigated. In addition, the possibility that copying ability might be associated with survival in the general population needs further study and more extensive neuropsychological investigation of parietal lobe function than performed with the CAMCOG may add to the validity of the measurements.

We conclude that parietal lobe function, assessed with a simple test of copying ability, is strongly associated with survival in AD, independent of demographic characteristics and general dementia severity. These results support the concept of relevant subgroups in AD in relation to survival, defined by parietal lobe function. Furthermore, our study suggests that the course of AD is more benign in women than in men.

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