Abstract  Objective Several predictors of Alzheimer’s disease (AD) have been identified. However, the relevance and independent contribution of risk factors and of possible early signs such as mild cognitive impairment and subjective memory impairment on the development of AD has not been investigated prospectively in a cohort of non-demented elderly including first-degree relatives of AD subjects. Method The development of AD was investigated in 757 non-demented elderly. Initial diagnoses were made from personal interviews. Information on 633 subjects after 4.7 ± 1.2 years (mean ± SD) was obtained either from personal or family history interviews. Using forward logistic regression analysis, predictors were identified by comparing their presence in 38 subjects who developed AD and 577 subjects who remained non-demented. Results The most important predictors of later Alzheimer’s disease were increased age (Odds ratio OR = 1.086/additional year, p < 0.001), initial subjective memory complaints (OR = 2.68, p = 0.019), initial mild cognitive impairment (OR = 2.51, p = 0.032) and female gender (OR = 2.84, p = 0.069). Exploratory analysis revealed that previous depression after the age of 60 years (OR = 2.37, p = 0.033) and the presence of the apolipoprotein E4 allele (OR = 2.49, p = 0.043) individually predicted new AD during follow-up. A positive family history of AD (i.e. being a first degree relative of a subject suffering from AD) did not significantly influence the development of AD (p > 0.2). Conclusions Increased age, the presence of mild cognitive impairment, subjective memory impairment and gender are the most relevant independent predictors of later Alzheimer’s disease that may be used in combination for clinical prediction of AD.

Key words Alzheimer’s disease · risk factors · mild cognitive impairment · subjective memory impairment · depression

Introduction

Alzheimer’s disease (AD) is the most common cause of dementia in the elderly. Even though several treatment options are available, treatment is most often started too late, i.e. when considerable neuropathological changes have already occurred (Hulette et al. 1998). However, a prerequisite for early intervention is to discriminate subjects who will later develop AD and those who will not (Soininen et al. 1998). This discrimination might be improved by a better knowledge of the relevance of putative risk factors and early signs of AD.

Several risk factors for AD have been observed, the most relevant being increased age (Andersen et al. 1999a, 1999b; Gao et al. 1998; Kawas et al. 2000) and female gender (Fratiglioni et al. 1997; Geerlings et al. 1999; Letenneur et al. 1999; Small 1995). A gender effect, however, has not been found by all authors (Andersen et al. 1999b; Rocca et al. 1998), or was only present in specific age groups (Ruitenberg et al. 2001). Genetic risk factors, such as the apolipoprotein E 4 genotype, are also known to increase the risk of AD (Albert et al. 1996; Gomez-Isla et al. 1996; Petersen et al. 1997; Roses 1998; Slooter et al. 1998; Steffens et al. 1997; Weiner et al. 1999), but their contribution in high-risk samples is less clear. A positive family history of AD might indicate the relevance of genetic risk factors, even if these are not yet identified (Breitner and Folstein 1984; Heun et al. 2001; Mohs et al. 1987; Payami et al. 1997; Silverman et al. 1994). Other authors, however, did not find a positive family history of AD to be a sufficient predictor of the development of AD (Launer et al. 1999; Small et al. 1995). These differences might be partially explained by the variance in the defi-
tions of a positive family history of AD, i.e. such as having one relative with AD in variable numbers of relatives of different age.

Early signs of AD might be the presence of mild cognitive impairment (Almkvist et al. 1998; Bozoki et al. 2001; Daly et al. 2000; Devanand et al. 1997; Doody et al. 2001; Flicker et al. 1991; Geerlings et al. 1999; Morris et al. 2001; Petersen et al. 1999; Petersen et al. 2001; Sramek et al. 2001), or of subjective memory impairment (Geerlings et al. 1999). Most of these studies examined a limited set of risk factors and did not look at possible interactions. Consequently, it is not clear whether subjective memory impairment is relevant for the prediction of AD in addition to the effect of mild cognitive impairment on the risk. Subjective memory impairment has been assumed to be more characteristic of depression and pseudodemencia than of dementia; the major clinical impact assumed to be more characteristic of depression and pseudodemencia than of dementia; the major clinical impact of mild cognitive impairment is relevant for the prediction of AD.

The relevance of these risk factors or early signs might be different for clinical and population samples (Jorm et al. 1997; Ritchie et al. 2001). However, the relevance of different risk factors has not yet been confirmed in an elderly cohort that included first-degree relatives of carefully examined AD subjects. Consequently, we examined the relevance of risk factors and early signs in a prospective cohort of non-demented elderly including first-degree relatives of AD subjects. Being identified as a first-degree relative of an examined AD patient is a more precise and less questionable indicator of a positive family history of AD than the history of dementia in family member.

Risk factors and initial signs of AD selected for the present study were age, female gender, a positive family history for AD (i.e. the subject being a first-degree relative of a subject suffering from AD), the presence of an apolipoprotein E4 allele, the presence of mild cognitive impairment, of subjective memory complaints and a history of geriatric depression (age at onset >60 years). The comparison of the initial characteristics of subjects with new AD at follow-up with subjects who had remained non-demented allowed the evaluation of the predictive validity of initially assessed risk factors and early signs of AD.

**Subjects and methods**

**Subject recruitment**

All non-demented subjects (defined by the absence of dementia according to DSM-III-R criteria (American Psychiatric Association 1987) above the age of 55 years, who had been carefully examined for possible initial signs of dementia and for the presence of possible risk factors during a previous comprehensive family study, were selected for the present prospective cohort study. The study has been performed in agreement with the declaration of Helsinki, the design was approved by the ethics committees of the Universities of Mainz and Bonn, all patients and relatives gave full written consent for participation after having been completely informed on the study procedures.

Recruitment strategies and results of the initial family study sample including possible selection bias have already been published (Heun et al. 1995, 2001). Briefly, patients with Alzheimer’s disease (AD) and/or major depression (according to DSM-III-R criteria, APA 1987)39 over 60 years had been consecutively recruited from the Inpatient Departments of Psychiatry of the University of Mainz (recruitment from 1992 to 1995) and of the University of Bonn (recruitment from 1996 to 1998). Control subjects who were group-matched to the patient sample for age, gender, and educational background had been recruited with the support of the cities’ census agencies. The patients and controls had been asked to provide names and addresses of all first-degree relatives. For the purpose of the family study, patients and controls had to have at least one first-degree relative aged 55 or older who was available for an interview. The initial family study sample included 78 subjects with AD, 78 with early-onset depression, 74 with late-onset depression (onset age > 60 years), 53 with histories of both AD and depression (co-morbid patients) and 162 control subjects from the general population (including 22 subjects with AD and 17 subjects with a lifetime diagnosis of major depression). The 445 personally interviewed study subjects had had 3002 first-degree relatives. Information on 210 (7%) of these relatives was unavailable. Of the remaining 2792 relatives, 1236 (44.3%) were deceased (Table 1); 775 (49.5%) of the remaining relatives could be interviewed.

To assess the relevance of positive predictors of AD for the present study, all 757 initially non-demented and personally interviewed subjects of the family study sample aged above 55 years (out of 775 interviewed family members and 162 interviewed subjects from the general population) were selected for the present prospective cohort study. Subjects either with a MMSE score below 24, a Hachinski Ischemic score above 2, a history of dementia or other major medical disorder possible to cause depression or depression were excluded from this follow-up study. The follow-up study was performed between 1999 and 2001 in Bonn and Mainz. To cover a large time span for survival analyses, those examined last during the initial family study were examined first during follow-up, and vice versa. Thus, the time span between both examinations ranged from 2 up to 10 years, the mean follow-up period was 4.7 ± 1.2 years.

**Diagnostic assessment during the initial assessment**

All first-degree relatives and control subjects were assessed using the Composite International Diagnostic Interview (CIDI, World Health Organization 1990) to assign lifetime DSM-III-R diagnoses for major psychiatric disorders (American Psychiatric Association 1987). To detect and diagnose dementia, patients, controls and their relatives were interviewed using the Structured Interview for Diagnosis of Dementia of the Alzheimer Type, Multi-infarct Dementia, and Dementia of other Aetiology (SIDAM, Zaudig et al. 1991), which includes the Mini Mental State Examination (MMSE, Folstein et al. 1975) and the Hachinski Ischemia Scale (Hachinski et al. 1975).

To detect depression and dementia in relatives, we additionally used the Family History Questionnaire (Andreasen et al. 1977) and the Family Dementia Risk Questionnaire (Breitner and Folstein 1984; Silverman et al. 1986). Family history information from spouses as well as from all interviewed relatives was obtained, if possible. The interviewers were carefully trained medical students in their final year of training or junior physicians.

After reviewing all available information, final diagnoses and age-at-onset for the initial family study and again, independently, for the follow-up study were assigned according to the consensus judgement of two experienced psychiatrists who remained blind to the identity of all probands and relatives using the best-estimate procedure (Leckman et al. 1982).

Interrater reliability of the direct interview data and of family history information were good for AD (Cohen’s $\kappa = 1.0$, CI 0.781–1.0 and $\kappa = 0.82$, CI 0.61–1.0, respectively, independent interviews in both cases; Heun et al. 1998, Ptok et al. 2001).