Course of minimal dementia and predictors of outcome

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SUMMARY

Background Previous studies have indicated that not all subjects who meet the CAMDEX criteria of ‘minimal dementia’ progress to dementia. In the present study, predictors of outcome in minimally demented subjects were tested.

Methods Forty-five subjects with minimal dementia who were participating in a population-based study were followed-up for on average 2.3 years. Variables tested as predictors of outcome were age, the apolipoprotein E (APOE) genotype, and the baseline scores on the MMSE, CAMCOG memory subscale, and fluency. Depression at baseline was tested as a predictor of reversible minimal dementia.

Results At follow-up, minimal dementia turned out to be reversible in 11 subjects (24%), and persistent in ten subjects (22%). Twenty-four subjects (53%) had become demented. Predictors of outcome in multivariate analyses were age, score on the CAMCOG memory subscale, and the APOE genotype. Depression was not associated with reversible minimal dementia.

Conclusions Subjects who meet the CAMDEX criteria of minimal dementia form a heterogenous group with respect to clinical outcome. Age, the score on the CAMCOG memory subscale, and the APOE genotype can improve predictive accuracy in these subjects. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — minimal dementia; population-based study; prospective study; mild cognitive impairment

INTRODUCTION

The Cambridge Mental Disorders of the Elderly Examination (CAMDEX) uses the term ‘minimal dementia’ for subjects with mild cognitive impairment at high risk for dementia (Roth et al., 1986). Previous studies, however, indicated that not all subjects with minimal dementia progress to dementia (O’Connor et al., 1991; Cooper et al., 1996). It was shown that 25% of the subjects with minimal dementia improved at follow-up such that minimal dementia was no longer present, about 25% of the subjects remained minimally demented, and 50% of the subjects had become demented (O’Connor et al., 1991; Cooper et al., 1996). It would be useful to have predictors of outcome in these subjects because subjects at high risk for dementia may be candidates for drug therapy that could improve the cognitive impairment or slow down the neurodegenerative process. In addition, the caregivers of these subjects may benefit from counseling on how to handle the cognitive impairment of their partners, relatives, or friends. Predictors of outcome in subjects with minimal dementia, however, have not yet been tested. Because the CAMDEX is a widely used instrument in both clinical and epidemiological settings, information on predictors of outcome in minimally demented subjects may be relevant to many workers in the field of old-age psychiatry and neurology. In the present longitudinal study of subjects with minimal dementia, we tested a number of variables that, in non-demented elderly, have been associated with an increased risk of dementia or cognitive decline, namely, age (Ott et al., 1998), the apolipoprotein E (APOE) genotype (Petersen et al., 1995), memory function e.g. (Kluger et al., 1999; Nielsen et al., 1999; Visser et al., 2000a, b), fluency e.g. (Nielsen et al., 1999;
Visser et al., 2000b), and the score on the Mini-Mental State Examination (MMSE) (Braekhus et al., 1995; Visser et al., 2000a). The presence of depression at baseline was tested as a predictor of reversible minimal dementia because previous studies have indicated that improvement of depression is associated with reversibility of cognitive impairment (Abas et al., 1990; Hill et al., 1992).

METHODS

Subjects

The subjects with minimal dementia were selected from a cohort of 527 subjects of the Amsterdam Study of the Elderly (AMSTEL) who were participating in a 3-year follow-up study. The AMSTEL study is a two-stage population-based study of mental functioning in 4051 non-institutionalized people aged 65–85 years living in Amsterdam, the Netherlands (Launer et al., 1993). From the 4051 members of the baseline cohort, we excluded those (n = 95) who were nearly blind, or deaf, or did not have a thorough command of the Dutch language. From the remaining 3956 subjects, we invited for follow-up all respondents (n = 156) who scored less than 22 points on the Mini Mental State Examination (MMSE) (Folstein et al., 1975), a random age-stratified sample (5-year strata, 65–69 to 80–84 years) of approximately 45% (n = 416) of subjects with borderline scores (22–26 points) on the MMSE, and a random age-stratified sample of approximately 7% (n = 215) of subjects with good (27–30 points) MMSE scores (Jonker et al., 1998). Of the 787 subjects who were invited, 527 individuals (67%) agreed to participate. Compared with the respondents, the nonrespondents to the follow-up study did not differ in age, sex distribution, MMSE score, or years of education. Of the 527 subjects who participated, 80 subjects had minimal dementia at baseline. Minimally demented subjects who had an history of stroke (n = 11) and/or Parkinson’s disease (n = 7) were excluded at baseline. The study cohort consisted of 63 subjects. All subjects gave their informed consent prior to inclusion in the study.

Baseline assessment and clinical diagnosis

Each subject was assessed for dementia by means of an examination conducted at home by a research nurse and a physician. The assessment included a questionnaire, cognitive tests, and a clinical examination with the validated Dutch version of the CAMDEX protocol (Roth et al., 1986; Derix et al., 1992). An informant interview was administered to the closest relative or caregiver. The diagnosis of minimal dementia was made when, according to the overall clinical impression, there was limited and variable impairment in cognitive and social functioning, such as difficulty with learning and recalling events, a tendency to misplace possessions, and minor errors in orientation, while the DSM-III-R criteria of dementia were not met (Roth et al., 1986; O’Connor et al., 1991). The diagnoses of dementia and Alzheimer’s disease were made according to the DSM-III-R (American Psychiatric Association, 1987), and NINCDS-ADRDA criteria (McKhan et al., 1984), respectively. The diagnosis of depression was made according to the CAMDEX criteria (Roth et al., 1986).

Cognitive measures

The MMSE is a measure of global cognitive impairment and has a maximum score of 30. The CAMCOG is the cognitive section of the CAMDEX. The maximum score is 107. Memory was tested with the CAMCOG memory subscale (maximum score of 33). The fluency score consisted of the number of animals named in 1 minute. Because age, sex, and education may influence cognitive performance, we performed all analyses with and without correction for these variables. The correction was based on the baseline cognitive scores of the non-demented subjects who were also non-demented at the 3-year follow-up (Visser et al., 1999). Since the results of both analyses were similar, we only present the uncorrected cognitive scores.

Follow-up

Subjects were reassessed annually for 3 years according to the CAMDEX protocol.

Apolipoprotein E phenotyping

The APOE phenotypes were determined by isoelectric focusing of delipidated plasma samples, followed by immunoblotting (Havekes et al., 1987). Since the APOE phenotypes are the same as the APOE genotypes, we will refer to them as APOE genotypes. Blood samples were not available for four minimally demented subjects. The baseline characteristics of minimally demented subjects with or without blood samples were similar. We classified the subjects according to the presence of an APOE-e4 allele in two groups: subjects with at least one APOE-e4 allele (APOE-e4+ group) and subjects with no APOE-e4 allele (APOE-e4- group).
**Statistical analysis**

The data were analyzed using SPSS for the Macintosh 4.0 (SPSS Inc., Chicago, IL, USA). Group comparisons with continuous variables and a group size of 10 or larger were carried out with a t-test. Group comparisons with continuous variables and a group size smaller than 10 were analyzed with the Mann–Whitney test corrected for ties. Categorical data were analyzed with a Chi square test with continuity correction. When at least one cell had an expected frequency less than 5, the two-tailed Fisher’s exact test was applied. Logistic regression analysis was performed to identify variables that were predictors of outcome. At the first step, age, sex, education, the APOE variable (APOE-e4+/APOE-e4−), the depression variable (present/absent), and the scores on the MMSE, CAMCOG memory subscale, and fluency were entered, and variables were selected that were significantly associated with outcome with backward step selection using the Likelihood Ratio test with \( p = 0.10 \) as criterion to remove variables. The CAMCOG total score was not entered in the logistic regression analysis because this score included the scores for the MMSE, memory subscale, and fluency and, for this reason, correlated highly with these scores. All statistical tests were two-tailed. The significance level was set at 0.05.

**RESULTS**

Forty-five subjects (71%) completed the first follow-up assessment, 41 subjects (65%) completed the second follow-up assessment, and 34 subjects (54%) completed the third follow-up assessment. Fourteen subjects (22%) refused all follow-up assessments and four subjects (6%) had died before the first follow-up assessment. The baseline characteristics of the subjects with at least one follow-up and with no follow-up did not differ significantly from each other (Table 1). The average follow-up was 2.3 years (SD 0.77). The reason why cognitive outcome was not available for subjects at the second or third follow-up assessment was refusal to participate \((n = 8)\) or death \((n = 3)\). We classified the 45 subjects according to the latest available outcome.

**Course of minimal dementia**

Minimal dementia turned out to be reversible in 11 subjects (24%), persistent in 10 subjects (22%), and progressive in 24 subjects (53%). Of the subjects with dementia at follow-up, 16 (67%) had mild dementia and eight (33%) had moderate dementia at follow-up. The type of dementia was Alzheimer-type dementia in 19 subjects (79%), vascular dementia in one subject (4%), and other types of dementia in four subjects (17%). Fourteen subjects had become demented at the first follow-up assessment, four subjects at the second follow-up assessment, and six subjects at the third follow-up assessment. Subjects with dementia after 1 year were older and had lower memory scores at baseline than subjects who had become demented at the second or third follow-up assessment. There were no differences in baseline characteristics between subjects who had become demented at the second or third follow-up assessment.

**Predictors of outcome**

The baseline characteristics according to outcome are presented in Table 2. Subjects with reversible minimal dementia were younger and had better memory performance at baseline than the subjects who were demented at follow-up. There were no statistically significant differences in baseline characteristics between subjects with persistent minimal dementia and subjects with dementia at follow-up (Table 2).

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics</th>
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</thead>
<tbody>
<tr>
<td>Total sample ((n = 63))</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Male/Female (% male)</td>
</tr>
<tr>
<td>Education (years)</td>
</tr>
<tr>
<td>APOE-e4+/APOE-e4− (% APOE-e4+)</td>
</tr>
<tr>
<td>Depressed/Not depressed (% depressed)</td>
</tr>
<tr>
<td>MMSE score</td>
</tr>
<tr>
<td>CAMCOG total score</td>
</tr>
<tr>
<td>CAMCOG memory score</td>
</tr>
<tr>
<td>Fluency</td>
</tr>
</tbody>
</table>

All data are mean (SD) except for the variables sex, APOE, and depression for which the number of subjects (%) are indicated.
Predictors for reversible minimal dementia in the multivariate analysis were evaluated by comparing group I (reversible minimal dementia) in Table 2 with group II (persistent minimal dementia), and group III (dementia at follow-up). Only the baseline score on the CAMCOG memory subscale (odds ratio (OR) 1.3 (95% confidence interval (CI) 1.1–1.5) per unit change, \( p = 0.01 \)) was retained in the model after backward step selection. The sensitivity of the model (i.e. the chance that subjects with reversible dementia had a predicted probability of reversible minimal dementia greater than 0.50) was 36%, the specificity (i.e. the chance that subjects with no reversible dementia had a predicted probability of reversible minimal dementia less than 0.50) 91%, the positive predictive value (PPV) (i.e. the chance that subjects with a predicted probability of reversible minimal dementia greater than 0.50 indeed had reversible minimal dementia) was 57%, and the negative predictive value (NPV) (the chance that subjects with a predicted probability of reversible minimal dementia lower than 0.50 did not have reversible minimal dementia) was 81%.

Predictors for dementia were evaluated by comparing group III (dementia at follow-up) in Table 2 with group I (reversible minimal dementia) and group II (persistent minimal dementia). Age (OR 1.2 (95% CI 0.97–1.4) per unit change, \( p = 0.11 \)), the APOE variable (OR 3.6 (95% CI 0.7–19), \( p = 0.11 \)), and the baseline score on the CAMCOG memory subscale (OR 0.84 (95% CI 0.72–0.99) per unit change, \( p = 0.04 \)) were retained in the model after backward step selection. The sensitivity of the model was 65%, the specificity was 76%, the PPV was 75%, and the NPV was 67%.

Table 2. Baseline characteristics according to outcome

<table>
<thead>
<tr>
<th></th>
<th>No dementia at follow-up</th>
<th>Minimal dementia at follow-up</th>
<th>Dementia at follow-up</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>I vs II</td>
</tr>
<tr>
<td>N</td>
<td>11</td>
<td>10</td>
<td>24</td>
<td>0.40</td>
</tr>
<tr>
<td>Age</td>
<td>77.2 (4.9)</td>
<td>79.0 (4.6)</td>
<td>80.5 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Male/Female (% Male)</td>
<td>5/6 (45)</td>
<td>3/7 (30)</td>
<td>6/18 (25)</td>
<td>0.78</td>
</tr>
<tr>
<td>Education</td>
<td>2.7 (1.7)</td>
<td>2.9 (1.3)</td>
<td>2.6 (1.2)</td>
<td>0.79</td>
</tr>
<tr>
<td>APOE-e4+/APOE-e4− (% APOE-e4+)</td>
<td>3/8 (27)</td>
<td>3/7 (30)</td>
<td>12/11 (52)</td>
<td>1.0</td>
</tr>
<tr>
<td>Depressed/Not depressed (% depressed)</td>
<td>1/10 (9)</td>
<td>1/9 (10)</td>
<td>3/21 (13)</td>
<td>1.0</td>
</tr>
<tr>
<td>MMSE</td>
<td>23.2 (3.0)</td>
<td>22.1 (4.5)</td>
<td>23.0 (3.5)</td>
<td>0.52</td>
</tr>
<tr>
<td>CAMCOG total score</td>
<td>74.7 (10.6)</td>
<td>76.2 (11.1)</td>
<td>72.0 (11.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>CAMCOG memory score</td>
<td>18.2 (4.3)</td>
<td>15.4 (4.5)</td>
<td>12.6 (4.4)</td>
<td>0.16</td>
</tr>
<tr>
<td>Fluency</td>
<td>12.3 (4.2)</td>
<td>13.0 (7.2)</td>
<td>11.1 (4.6)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

All data are mean (SD) except for the variables sex, APOE, and depression for which the number of subjects (%) are indicated.

The relation between age, baseline score on the CAMCOG memory subscale, the APOE genotype, and outcome is presented in Figure 1. Because subjects with a diagnosis of dementia after 1 year had different baseline characteristics compared to the subjects with a diagnosis of dementia after 2 or 3 years, these subjects have been indicated separately. On the basis of the figure, the following decision rules for predicting outcome could be constructed. Age \( \leq 78 \) years and a baseline score on the CAMCOG memory subscale \( \geq 19 \) were the best predictors of reversible minimal dementia. The sensitivity of the cut-off scores for detecting subjects with reversible minimal dementia was 55%, the specificity 91%, the PPV 67%, and the NPV 86%. Age \( > 75 \) years and a baseline score on the CAMCOG memory subscale \( < 19 \) were the best predictors of dementia. The sensitivity of the cut-off scores for detecting subjects with dementia was 83%, the specificity 57%, the PPV 69%, and the NPV 75%. Age \( \geq 78 \) years and a baseline score on the CAMCOG memory subscale \( \leq 12 \) could accurately identify subjects with dementia after 1 year. The sensitivity of the cut-off scores for detecting subjects with dementia within 1 year was 86%, the specificity 94%, the PPV 86%, and the NPV 94%.

DISCUSSION

This study demonstrated that 24% of the subjects with minimal dementia had reversible minimal dementia at follow-up, 22% had persistent minimal dementia at follow-up, and 53% had become demented. Age, the score on the CAMCOG memory subscale at baseline, and the APOE genotype could predict outcome.
The outcome of subjects with minimal dementia is similar to that reported in other population-based prospective studies of minimal dementia (Cooper et al., 1996; O'Connor et al., 1991). O'Connor et al. (1991) showed in a two-year follow-up study of 24 minimally demented subjects that 21% had reversible minimal dementia, 29% had persistent minimal dementia, and 50% had become demented and at follow-up. Cooper et al. (1996) reported that 38% of the 53 subjects with minimal dementia at baseline had progressed to dementia after 2 years, while the other subjects remained minimally demented or had improved. In the present study, the cognitive scores of the subjects with persistent minimal dementia declined at follow-up, although this decline was less severe than that seen in subjects with dementia at follow-up (data not shown). Therefore, subjects who remain minimally demented at follow-up may become demented later, but longer follow-up studies are necessary to establish the definite outcome in these subjects.

The finding that memory scores, age, and the APOE genotype could predict outcome in minimally demented subjects is consistent with the findings from other prospective studies of subjects with mild cognitive impairment (Petersen et al., 1995; Kluger et al., 1999; Nielsen et al., 1999; Visser et al., 2000a,b). In contrast to other studies, we found that neither the baseline score on the MMSE nor the fluency performance was associated with outcome (Brækhus et al., 1995; Nielsen et al., 1999; Visser et al., 2000a,b). One possible explanation is that the inclusion criteria of minimal dementia selected a population that was more homogeneous with respect to these scores than in the other studies.

Depression was not associated with reversible minimal dementia. Four out of seven depressed subjects developed dementia even though the depression improved in three of them (data not shown). We have made a similar observation in depressed subjects with memory impairment who attended a memory clinic (Visser et al., 2000a,b). In another study, it was shown...
that depressive symptoms were as common in memory-impaired subjects who developed Alzheimer-type dementia at follow-up as in subjects with none-progressive cognitive impairment (Tierney et al., 1999). O’Connor et al. reported on two minimally demented subjects with depression at baseline in whom the cognitive impairment was thought to be related to their depression (O’Connor et al., 1991). However, the depression improved in these subjects while their cognitive functioning deteriorated. Taken together, these findings suggest that if cognitive impairment coexists with depression, the cognitive impairment is not simply secondary to the depression.

On the basis of Figure 1 we formulated decision rules for predicting outcome that may be useful in clinical practice. These rules, however, need cross-validation. Most subjects who were younger than 79 years and had high memory scores had reversible minimal dementia. However, one-third of the subjects predicted to have reversible minimal dementia did not have it. In these subjects, assessment of medial temporal lobe atrophy may further increase the predictive accuracy because it was shown that minimally demented subjects with normal memory scores who declined at follow-up had more atrophy of the medial temporal lobe than subjects who did not decline (Visser et al., 1999). Most subjects older than 75 years and with intermediate to low memory scores developed dementia at follow-up. However, one-third of the subjects predicted to have dementia did not have it and assessment of medial temporal atrophy may also be useful to improve predictive accuracy in these subjects. The combination of age older than 85 years and low memory scores could accurately identify a subgroup of demented subjects who became demented within 1 year. Two subjects (15%) fulfilling these criteria had persistent minimal dementia but their cognitive performance had declined severely (data not shown). Therefore, minimally demented subjects who are 78 years or older and who have low memory scores are at high risk to become demented and may be candidates for drugs that are used in the treatment of dementia.

One of the limitations of the study is that about 30% of the subjects had no follow-up assessment. This is not uncommon in population-based prospective studies of elderly subjects (Herlitz et al., 1997; O’Connor et al., 1991). Since the baseline characteristics of the subjects with no follow-up were similar to those who had at least one follow-up, it seems unlikely that selective attrition had occurred. About half of the subjects with reversible minimal dementia or persistent minimal dementia did not complete the 3-year follow-up. It seems unlikely that selective attrition had occurred because the baseline characteristics and follow-up cognitive scores did not differ between subjects with a 3-year follow-up and subjects with only a 1- or 2-year follow-up (data not shown). Further limitations are that a 3-year follow-up is probably too short to establish the definite outcome and that the small group size limited the power of the study. The community setting makes the diagnosis of dementia less accurate compared to that in a clinical setting. Still, all demented subjects (n = 11) who had one or two (n = 6) follow-up assessments after the diagnosis of dementia had been made, were also diagnosed as demented at these follow-up assessments. The diagnosis of dementia type was changed in one subject at a later follow-up assessment. Finally, it remains to be seen whether the findings from this population-based sample apply in a clinical setting.

In conclusion, the diagnosis of minimal dementia is made in mildly cognitively impaired subjects who form a heterogeneous group with respect to clinical outcome. Age, the APOE genotype, and the score on the CAMCOG memory subscale may be helpful to increase predictive accuracy in these subjects. The fact that depression was not associated with reversible minimal dementia suggests that when cognitive impairment and depression coexist, the cognitive impairment is not necessarily secondary to the depression.

KEY POINTS
- Subjects with minimal dementia have a variable outcome at follow-up
- Age, the score on the CAMCOG memory subscale, and the APOE genotype can improve predictive accuracy in these subjects
- If cognitive impairment and depression coexist, the cognitive impairment is not necessarily secondary to the depression

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REFERENCES


