Independent Predictors of Cognitive Decline in Healthy Elderly Persons

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Background: Several studies have shown that individually memory, hippocampal volume, and motor measures presage the onset of dementia. It is unclear if these independently contribute to the prediction of mild cognitive impairment.

Objective: To determine the ability of memory, hippocampal volume, and a gait speed to independently predict cognitive decline in healthy elderly persons.

Design: A prospective, longitudinal, observational cohort study with a mean follow-up of 6 years.

Participants: One hundred eight optimally healthy elderly cognitively intact subjects.

Main Outcome Measures: Any cognitive impairment noted on the Clinical Dementia Rating Scale (score = 0.5) or persistent or progressive cognitive impairment. Cox modeling determined if time to onset of cognitive impairment was associated with baseline logical memory II test score (a measure of delayed recall), hippocampal volume (magnetic resonance imaging), or gait speed (time to walk 30 ft [9 m]) independent of age, sex, depression, or the allele producing the ε4 type of apolipoprotein E (APOE ε4).

Results: Questionable dementia occurred in 48 participants in a mean (SD) of 3.7 (2.4) years. This progressed to persistent cognitive impairment in 38 of these participants in a mean (SD) of 4.4 (2.4) years. Logical memory II test performance and hippocampal volume each predicted onset of questionable dementia, independent of age and sex. Time to walk 30 ft additionally contributed independently to the prediction of time to onset of persistent cognitive impairment. Possessing the APOE ε4 allele and depression did not enter either model significantly.

Conclusions: Models combining multiple risk factors should refine the prediction of questionable dementia and persistent cognitive impairment, harbingers of dementia. Individuals at risk for cognitive impairment may represent a high-risk group for intervention.

Arch Neurol. 2002;59:601-606

Alzheimer Disease (AD) is a formidable public health issue, affecting an estimated 12% of the population over the age of 65 years in the United States. Approaches that allow better anticipation of progression to dementia in healthy individuals would enhance current efforts aimed at preventing or slowing AD onset.

Several risk factors have been identified that predict the onset of AD and cognitive impairment in elderly populations. The strongest include age, sex, educational level, genetic makeup (family history of dementia or allele producing the ε4 type of apolipoprotein E [APOE ε4]), mild cognitive impairment (MCI) (especially memory loss), parkinsonism, gait impairment, and hippocampal or medial temporal volume measures.

The present study was aimed at integrating several individually validated predictors of cognitive decline to determine if they independently predict decline in a group of initially healthy elderly persons. We examined clinical measures of memory, timed gait, and hippocampal volume. We hypothesized that models combining these measures could refine our ability to forecast the likelihood of progression to questionable dementia (QD) or persistent cognitive impairment (PCI), harbingers of AD, and candidates for clinical trials aimed at preventing the onset of AD.

RESULTS

Outcomes of 108 participants (68 women and 40 men) followed up for a mean of 6 years from the Oregon Brain Aging Study were examined. Ninety-seven percent were...
PARTICIPANTS AND METHODS

PARTICIPANTS

The Oregon Brain Aging Study is a prospective study of neurologic function in the optimally healthy elderly population. Subjects were 65 years or older at the initial assessment, without comorbid conditions, mentally healthy (normal) by mental status examination, and without memory impairment by self-report or proxy.18 None of the cohort had a history of significant head trauma, risk factors for vascular disease, or abuse of alcohol or other substances based on medical history or medical record review. Clinical examination findings and laboratory study results that included a complete blood cell count, chemistry profile, vitamin B12, and folate levels, chest x-ray film, and electrocardiogram were additionally used to exclude covert medical conditions that might contribute to cognitive impairment. At the time of recruitment, participants were taking only vitamins, hormone replacement therapy, and/or nonsteroidal anti-inflammatory drugs. Use of drugs that might affect cognitive function, including aspirin and vitamin E, coenzyme Q, nonsteroidal anti-inflammatory agents, and gingko biloba was recorded. Each participant underwent evaluation at 6-month intervals using standardized assessment tools and annual neurologic and neuropsychological assessments, and magnetic resonance imaging using previously described protocols.6,12

Survival analyses were done using the Cox proportional hazards model to determine if individual traits at study baseline could predict the earliest signs of cognitive decline or persistent impairment. Age, sex, educational level, depressive symptoms, APOE status (any ε4 allele), neuropsychological measures of memory and hippocampal volume, and gait measures were considered as potential explanatory variables. Length of follow-up was determined for all participants and each individual was classified as having attained 1 of the 3 study end points—QD, PCI, or censored status:

- Questionable dementia was identified in any subject who demonstrated a CDR score of 0.5 or more at any visit after the initial assessment irrespective of their ultimate outcome. We considered this a marker of increased risk of subsequent decline to PCI.
- Persistent cognitive impairment was defined as a conversion to a CDR score of 0.5 or more without a subsequent reestablishment of normal cognitive function (CDR=0).
- If subjects died following conversion, they were retained in this group.
- Those who did not demonstrate progression toward cognitive impairment (CDR score remained at 0) or either died or withdrew from the study prior to measurable progression were included in the analysis as censored cases.

Two regression analyses were run to model QD and PCI. The effects of age and sex were controlled for by entering them into the model at the first step. Hippocampal volumetric measures, memory scores, APOE ε4 level status, depressive symptoms, and motor measures were added by forward stepwise regression. With the exception of sex and age, variables are only reported if the survival model–calculated P values were less than .05 in 1 of the models examined. The interdependence of the predictor variables (age, LM II test score, time to walk 30 ft [9 m], and hippocampal volume) was further examined by calculating the partial correlation coefficients among these 4 variables.

Logical memory II test scores were determined for the Wechsler Memory Scale–Revised and the Wechsler Adult Intelligence Scale–Revised that was administered annually but was not used to determine dementia status.14 The logical memory (LM) test from the Wechsler Memory Scale–Revised and the Wechsler Adult Intelligence Scale–Revised that was administered annually but was not used to determine dementia status.14 The logical memory (LM) test from the Wechsler Memory Scale–Revised, in particular, included a brief story that was read to the subject and then scored for recall both immediately (LM I) and again 25 to 30 minutes later (LM II). Gait was evaluated annually by a neurologist (J.A.K., R.C., or colleagues) as part of a comprehensive neurologic examination and was quantified by having the participant walk at a self-selected pace 15 ft (4.5 m) out to a marker on the ground, turn, and walk back to the starting point. The time (seconds) and the number of steps (excluding steps taken to turn) were recorded.30

Magnetic resonance imaging scans were obtained near the time of enrollment using a 1.5-T scanner (GE Medical Systems, Milwaukee, Wis), with the following image parameters: multiecho multiplanar, 4-mm coronal slices; field of view, 24 cm²; acquisition matrix, 256 × 256 pixels; number of excitations, 0.5; repetition time, 3000 milliseconds; and echo times, 30 and 80 milliseconds. Image analysis was performed by semiautomated recursive segmentation using the program REGION (Oregon Aging and Alzheimer Disease Center, Portland) and by manual tracing using the National Institutes of Health Image (Version 1.5; National Institutes of Health, Bethesda, Md) on Macintosh computers (Apple Computers, Cupertino, Calif).12 Total pixel counts for each region (intraparenchymal and hippocampal areas) were summed for each slice and multiplied by the slice thickness to convert areas to volumes. Hippocampal volumes were measured by manually tracing the area between the red nucleus and the superior colliculus on serial slices using the National Institutes of Health Image. These analysis techniques have been previously shown to be reliable: for hippocampal volume, intraclass correlation = 0.90; for the measurement of intracranial volume, intraclass correlation = 0.98.12

DATA ANALYSIS

Baseline characteristics were compared using t or χ² tests. Survival analyses were done using the Cox proportional hazards model to determine if individual traits at study baseline could predict the earliest signs of cognitive decline or persistent impairment.
Table 1. Characteristics of Participants at Baseline and at the Time Questionable Dementia (QD) or Persistent Cognitive Impairment (PCI) Developed

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N = 108)</th>
<th>Participants With ND (n = 60)</th>
<th>Participants With QD (n = 48)</th>
<th>Participants With PCI (n = 38)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At entry</td>
<td>83.2 (7.9)</td>
<td>80.7 (8.2)</td>
<td>86.2 (6.3)†</td>
<td>86.4 (6.8)§</td>
</tr>
<tr>
<td>At onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, No. of participants</td>
<td>Male 40</td>
<td>26</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Female 68</td>
<td>34</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>Educational level, No. of years</td>
<td>14.1 (2.8)</td>
<td>14.0 (2.7)</td>
<td>14.2 (2.9)</td>
<td>14.1 (2.9)</td>
</tr>
<tr>
<td>SES [6-86]</td>
<td>48.0 (12.9)</td>
<td>48.4 (11.7)</td>
<td>47.6 (14.3)</td>
<td>47.6 (14.5)</td>
</tr>
<tr>
<td>Vocabulary level [0-70]</td>
<td>53.9 (9.9)</td>
<td>54.0 (9.5)</td>
<td>53.8 (10.4)</td>
<td>54.1 (11.1)</td>
</tr>
<tr>
<td>GDS score [0-30]</td>
<td>3.3 (2.7)</td>
<td>3.0 (2.7)</td>
<td>3.7 (2.8)</td>
<td>3.8 (2.9)</td>
</tr>
<tr>
<td>MMSE score [0-30]</td>
<td>28.1 (1.7)</td>
<td>28.4 (1.5)</td>
<td>27.6 (1.8)†</td>
<td>27.7 (1.8)</td>
</tr>
<tr>
<td>NCSE total score [0-87]</td>
<td>76.4 (6.4)</td>
<td>78.1 (5.6)</td>
<td>74.3 (6.7)†</td>
<td>74.4 (6.8)§</td>
</tr>
<tr>
<td>APOE ε4 present, No. of participants</td>
<td>24</td>
<td>14</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>No APOE ε4, No. of participants</td>
<td>84</td>
<td>46</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Onset, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>6.0 (2.6)</td>
<td>5.9 (2.6)</td>
<td>6.2 (2.6)</td>
<td>6.7 (2.4)</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD) unless otherwise indicated. ND indicates no dementia; ND; Hollingshead socioeconomic status; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; NCSE, modified Neurobehavioral Cognitive Status Examinations (total possible score); and APOE ε4, apolipoprotein E ε4 allele.
†All participants with PCI had previously met criteria for QD and are also included among the participants with QD.
‡P<.05, PCI vs ND.
§P<.05, PCI vs ND.
| Values in brackets indicate reference ranges. Higher scores indicate better performance, except for GDS, where higher scores indicate more depressive symptoms. |

Table 2. Mean Values for Predictor Variables*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Participants With ND</th>
<th>Participants With QD</th>
<th>Participants With PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM II test score [0-25]</td>
<td>9.9 (4.7)</td>
<td>11.0 (4.2)</td>
<td>8.6 (5.0)†</td>
<td>8.2 (4.9)†</td>
</tr>
<tr>
<td>Follow-up LM II test score [0-25]</td>
<td>10.5 (5.9)</td>
<td>13.3 (5.1)</td>
<td>6.9 (4.8)†</td>
<td>5.7 (4.5)†</td>
</tr>
<tr>
<td>Hippocampal volume, mm³</td>
<td>1313.5 (193.6)</td>
<td>1370.3 (178.9)</td>
<td>1242.5 (189.4)†</td>
<td>1240.0 (190.8)‡</td>
</tr>
<tr>
<td>Intracranial volume, cm³</td>
<td>1155.4 (125.7)</td>
<td>1167.2 (110.2)</td>
<td>1140.6 (142.6)</td>
<td>1144.0 (149.6)</td>
</tr>
<tr>
<td>Total brain volume, cm³</td>
<td>894.2 (98.0)</td>
<td>916.8 (81.8)</td>
<td>893.6 (108.3)§</td>
<td>888.1 (115.2)§</td>
</tr>
<tr>
<td>Timed walk test, s§</td>
<td>11.0 (3.3)</td>
<td>10.2 (2.3)</td>
<td>11.9 (4.1)†</td>
<td>12.2 (4.4)†</td>
</tr>
<tr>
<td>Measured timed walk test, No. of steps</td>
<td>18.3 (4.4)</td>
<td>17.6 (3.7)</td>
<td>19.2 (5.0)</td>
<td>19.0 (5.3)</td>
</tr>
<tr>
<td>Timed walk test, steps/s</td>
<td>1.74 (0.36)</td>
<td>1.75 (0.31)</td>
<td>1.72 (0.41)</td>
<td>1.66 (0.42)</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD) unless otherwise indicated. ND indicates no dementia; QD, questionable dementia; PCI, persistent cognitive impairment; and LM, logical memory. See the “Assessments” subsection of the “Participants and Methods” section for an explanation of the various tests used in this study. Values in brackets indicate reference ranges. Higher scores indicate better performance.
†P<.05, QD vs ND.
‡P<.05, PCI vs ND.

Table 1, 48 subjects had a rating of QD, while 38 had subsequently developed PCI. Patients with QD and PCI were older than those whose cognition remained intact. There was no difference between groups in the use of drugs that might affect cognitive function (P>.10 for all drugs), including ascorbic acid, vitamin E, coenzyme Q10, nonsteroidal anti-inflammatory agents, and gingko biloba. The Mini-Mental State Examination and Neurobehavioral Cognitive Status Examinations scores were higher at baseline in those whose cognition remained intact. Sex, educational level, vocabulary, socioeconomic class, APOE status, Geriatric Depression Scale score, and duration of follow-up did not differ between those whose cognition became impaired and those whose cognition remained intact.

Participants whose cognition became impaired had poorer recall on the LM II test, smaller hippocampal volumes, and took longer to walk 30 ft. Participants whose cognition became impaired (data not available for 3 QD and 3 PCI participants) with follow-up declined on the LM II test, while those whose cognition remained intact improved (data not available for 1 participant). The proportion of participants remaining intact who achieved a score of less than 5 (1.5 SDs) on the LM II test was 3 of 59, while 18 of the 45 participants with QD and 18 of the 35 participants with PCI showed this degree of impairment. Total brain, but not total intracranial volumes, were smaller in participants who became impaired (Table 2); however, these were not entered into the models.

Coefficients in the multivariable Cox models are listed in Table 3. Older age, a worse LM II test score,
and decreased hippocampal volume were significant predictors of QD. A 1-year increase in age yielded an increased risk (hazard ratio) of 1.07 times, while a 1-point increase in LM II test score yielded a decreased risk of 0.90, and a 1-cm³ increase in hippocampal volume yielded a decreased risk of 0.027. The LM II test score, hippocampal volume, and time to walk 30 ft were significant in the model for the development of PCI. A 1-point increase in the LM II test score yielded a decreased risk of 0.85 and a 1-cm³ increase in the hippocampal volume yielded a decreased risk of 0.036. A 1-second increase in time to walk 30 ft yielded an increased risk of 1.14 times of developing PCI. Age only approached statistical significance in this model and sex was not a significant predictor in either model.

Age was negatively correlated with hippocampal volume (partial \( r = -0.44 \)) and LM II test score (partial \( r = -0.23 \)) and positively correlated with time to walk 30 ft (partial \( r = 0.25 \)). The correlation between the other variables was weak (partial \( r < 0.1 \)), except for a negative correlation between hippocampal volume and time to walk 30 ft (\( r = -0.12 \)).

**COMMENT**

Our study combined memory performance, neuroimaging, and physical findings in one predictive model. Logical memory II test score, hippocampal volume, and time to walk 30 ft forecast cognitive decline, independent of age and sex, in this cohort of initially healthy elderly participants. Age was a significant risk for the development of QD only. Time to walk 30 ft only entered the model for the development of PCI.

A previous population-based study found that global cognitive function, age, and family report of memory loss were associated with subsequent cognitive decline. In another study, neuropsychological variables did not contribute to the prediction of dementia in subjects with reported memory losses. Memory measures combined with medial temporal volumes presaged dementia in elderly persons younger than 85 years. That memory performance and hippocampal volume independently contributed to the model in our study supports the observation that hippocampal atrophy does not serve as a surrogate for memory loss. This proposal is supported by the weak correlation between the predictor variables. In a study of younger elderly persons, memory measures and APOE genotype did not predict the development of AD, whereas the fusiform, middle, and inferior temporal gyral volumes had a sensitivity of 93%. Progressive brain atrophy, or functional imaging have also been examined in other studies.

Impaired gait independent of significant medical, orthopedic, or rheumatologic disease was a significant predictor only for the development of PCI, a persistent state of cognitive decline, which may be closer to dementia than QD. Another study has shown that a change in brain magnetic resonance imaging and APOE4 both predicted cognitive and lower extremity functional decline in an elderly male cohort. The presence of the APOE4 allele did not contribute significantly to our multivariable model, possibly reflecting the older age of the participants. That depressive symptoms were not significant predictors in our cohort (data not shown) might be related to the exclusion of participants with severe depressive symptoms at baseline, or to other selection criteria.

The identification of QD in this cohort puts individuals at risk for subsequent evolution to PCI at a rate consistent with the conversion to dementia reported in other studies. With longer follow-up, these individuals may progress to dementia. Questionable dementia represents a clinically definable end point that is independent of psychometric testing, unlike MCI. Both are precursors to dementia, but MCI was not examined in the current study since LM II test performance was examined as a predictor. It would be inappropriate to use the same psychological predictor as an end point since poor performance on memory testing at baseline would be expected to lead to poor subsequent memory performance.

Only a small portion (5%) of intact elderly persons achieved impairment on the LM II test of 1.5 SDs below norms for that age group, corresponding to MCI, with longitudinal follow-up. A higher proportion of QD (40%) and PCI (51%) showed this degree of impairment. These proportions are conservative because appropriate norms for longitudinally presented memory tests in this highly educated, very elderly population are unavailable. Nevertheless, these findings highlight the incomplete overlap between categories of cognitive impairment in elderly persons and point to the need to better define their significance in longitudinal cohort studies.

Gait impairment, which was a predictor of PCI, may indicate more widespread pathologic change, or the coexistence of vascular disease, either of which might accelerate the development of a more persistent state of cognitive impairment. We believe that the latter category merited definition as an irreversible state. Motor impairment has previously been described in association with cognitive impairment, but our data suggest that it can be observed prior to the development of cognitive decline in the oldest old.
By focusing on exceptionally healthy, very elderly volunteers, we were able to identify intrinsic characteristics associated with dementia risk without confounding medical conditions. The participants in our study represent the upper 1% to 3% of the elderly population in terms of health and, hence, our results cannot be generalized. Nevertheless, a broader age range of participants with representative medical conditions (eg, hypertension, diabetes mellitus) should be examined in future investigations to confirm our findings. Another strength is that most of our participants have agreed to brain autopsy, which will ultimately clarify the cause(s) of cognitive impairment. To date, patients with cognitive impairment (both QD and PCI) have met criteria for AD at autopsy, consistent with the experience of other investigators, and suggesting that these end points are clinically meaningful. Logical memory II test scores at baseline, in our study, were well above published criteria for MCI suggesting that our subjects were in a presymptomatic state rather than at an early phase of dementia. Others have provided evidence for a long preclinical phase for dementia. Future studies will examine the transition between QD to PCI and progression to subsequent dementia.

Assessment of risk factors for the development of cognitive impairment in elderly persons will need to include cognitive and motor measures as well as neuroimaging. A combined approach will be useful for studies targeting preventive therapies for those at highest risk prior to the onset of AD.

Accepted for publication December 19, 2001.

Author contributions: Study concept and design (Mr Marquis and Drs Howieson, Kaye, and Camicioli); acquisition of data (Ms Moore and Drs Howieson, Payami, Kaye, and Camicioli); analysis and interpretation of data (Mr Marquis, Ms Moore, and Drs Sexton and Camicioli); drafting of the manuscript (Mr Marquis and Drs Kaye and Camicioli); critical revision of the manuscript for important intellectual content (Mr Marquis, Ms Moore, and Drs Sexton, Payami, Kaye, Howieson, and Camicioli); statistical expertise (Mr Marquis, Ms Moore, and Drs Sexton, Payami, and Kaye); obtained funding (Drs Payami, Kaye, and Camicioli); administrative, technical, and material support (Dr Kaye); study supervision (Drs Kaye and Camicioli).

The Oregon Brain Bank and the Oregon Aging and Alzheimer Disease Center are supported by grants AG08017 and 3M01RR0334 from the National Institutes of Health; the Alzheimer Research Alliance of Oregon, Portland; the Medical Research Foundation of Oregon, Portland; and donations from individuals. The Oregon Brain Aging Study is additionally supported by a Merit Review Grant from the Department of Veterans Affairs, Washington, DC (Dr Kaye).

We thank the staff of the Oregon Aging and Alzheimer Disease Center and the Oregon Brain Aging Study.

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