Is Age-related Maculopathy Associated with Alzheimer's Disease?

The Rotterdam Study

Caroline C. W. Klaver,1,2 Alewijn Ott,1 Albert Hofman,1 Jacqueline J. M. Assink,1,3 Monique M. B. Breteler,1 and Paulus T. V. M. de Jong1,2,4

The authors examined the relation between age-related maculopathy and Alzheimer's disease in the Rotterdam Study, a prospective population-based study in the Netherlands. From 1990 to mid-1993, subjects aged 75 years or older (n = 1,438) were screened for the presence of age-related maculopathy and Alzheimer's disease, and follow-up examinations were conducted from mid-1993 to the end of 1994. Subjects with advanced age-related maculopathy at baseline showed an increased risk of incident Alzheimer's disease (relative risk = 2.1, 95% confidence interval: 1.1, 4.3; adjusted for age and gender), but this risk decreased after additional adjustment for smoking and atherosclerosis (relative risk = 1.5, 95% confidence interval: 0.6, 3.5). These findings suggest that the neuronal degeneration occurring in age-related maculopathy and Alzheimer's disease may, to some extent, have a common pathogenesis.


aging; Alzheimer disease; atherosclerosis; comorbidity; incidence; macular degeneration; neurodegenerative diseases; smoking

Age-related maculopathy and Alzheimer's disease are both chronic neurodegenerative disorders that affect a substantial proportion of elderly persons, imposing a significant burden on public health and quality of life. Among those aged 75 years or older in the Netherlands, 8 percent are affected by end-stage age-related maculopathy (1) and 13 percent are diagnosed with Alzheimer's disease (2). Characteristic of these disorders is the irreversible loss of neuronal function, for which there is no cure.

Although the etiology of both is largely unknown, the pathogeneses of age-related maculopathy and Alzheimer's disease show some striking similarities. In age-related maculopathy, early histopathologic manifestations are extracellular drusen deposits and basal laminar deposits. These lesions contain lipids, glycoproteins, and glycosaminoglycans, which are presumably derived from a degenerating neuroretina (3–6). Accumulation of these deposits is associated with deterioration of macular function and subsequent loss of photoreceptors (7–9). In Alzheimer's disease, an early pathologic hallmark is the presence of extracellular senile plaques. These plaques contain β-amyloid, activated microglia, and axons and dendrites from dystrophic neurons (10, 11). Analogous to those in age-related maculopathy, these deposits are associated with neuronal malfunction and cell loss (11–13).

The pathogenic parallels between age-related maculopathy and Alzheimer's disease prompted us to study their comorbidity within the population-based Rotterdam Study. This study was designed to investigate the determinants of various chronic geriatric disorders among middle-aged and elderly subjects. In the present analysis, we studied the relation of age-related maculopathy at baseline with the 2-year incidence of Alzheimer's disease among subjects aged 75 years or older.

MATERIALS AND METHODS

Study design and population

The Rotterdam Study is a population-based prospective cohort study conducted in a suburb of Rotterdam, the Netherlands, in which chronic neurologic, ophthalmologic, cardiovascular, and locomotor disorders are investigated (14). The study was approved by the Medical Ethics Committee of the Erasmus University Medical School. Informed consent and permission to retrieve information from physicians was obtained from all participants. Baseline interview and screening...
examinations took place from 1990 to mid-1993; follow-up examinations were conducted from mid-1993 to the end of 1994.

Of 10,275 eligible subjects in the entire Rotterdam Study, 7,983 (78 percent) of those aged 55 years or older agreed to participate in the baseline phase. In the present study, we included only those subjects aged 75 years or older (n = 2,016); of these, 1,599 (79 percent) underwent a complete screening for age-related maculopathy and Alzheimer's disease. A total of 139 subjects in this age group were diagnosed with prevalent Alzheimer's disease, while 22 subjects had a dementia other than Alzheimer's disease. Therefore, 1,438 subjects were at risk of incident Alzheimer's disease during the follow-up period and were included in the analysis.

Diagnosis

Case-finding procedures for age-related maculopathy and Alzheimer's disease have been described in detail elsewhere (1, 2). In brief, during the ophthalmologic screening examination, 35° color transparencies were taken of the macular area (Topcon TRV-50VT fundus camera; Topcon Optical Company, Tokyo, Japan). The diagnosis of age-related maculopathy was based on the grading of fundus transparencies according to the international classification system (15). Age-related maculopathy was stratified on the basis of four exclusive stages, which increased in clinical severity: no age-related maculopathy, the absence of any type of soft drusen and atrophic or neovascular macular degeneration; stage 1, the presence of only soft distinct drusen of more than 63 μm in the absence of pigmentary irregularities and atrophic or neovascular macular degeneration; stage 2, the presence of either distinct drusen with pigmentary irregularities or indistinct or reticular drusen; stage 3, the presence of indistinct or reticular drusen with pigmentary irregularities; and stage 4, the presence of either atrophic or neovascular end-stage macular degeneration. Best-corrected visual acuity was measured at a distance of 3 m by using a modified Early Treatment Diabetic Retinopathy chart.

Dementia screening and diagnosis at baseline and at follow-up followed a three-step protocol that included the Mini-Mental State Examination and the Geriatric Mental State schedule, the Cambridge Mental Disorder Examination (CAMDEX) diagnostic interview, and examination by a neurologist, as described previously (2). In addition, the entire cohort was monitored during follow-up to detect cases of dementia by linking the general practitioner's automated medical record system to the database of the Rotterdam Study. Data on subjects who could not be rescreened at follow-up (refusals, deceased) were obtained from inpatients, medical files, and the regional institute for outpatient mental health care. The final diagnosis of Alzheimer's disease was based on all collected information by using NINCDS-ADRDA criteria (16), which in brief imply the presence of dementia not caused by systemic or other brain disorders, deficits in at least two areas of cognition, gradual progression of disease, and no disturbance of consciousness.

Smoking, atherosclerosis, and apolipoprotein E

Smoking habits were assessed during the baseline home interview; subjects were stratified as noncigarette smokers, former cigarette smokers, and current cigarette smokers. The presence of generalized atherosclerosis was evaluated by using the ratio of ankle to brachial systolic blood pressure (17, 18), as described previously (19). Atherosclerosis was considered present when the left or right ankle-brachial index was less than 0.90. Genomic DNA was used for genotyping of apolipoprotein E. The apolipoprotein E gene was amplified by using the primers and conditions, as described (20, 21). Genotypes E2/E4, E3/E4, and E4/E4 were grouped and defined as the presence of the apolipoprotein E4 allele.

Statistical methods

The incidence of Alzheimer's disease was obtained for successive stages of age-related maculopathy. Person-years were calculated per age category after summation of each participant's contribution of follow-up time to each category. We calculated the relative risks of incident Alzheimer's disease for the four stages of age-related maculopathy as well as for low visual acuity by using Cox proportional hazards regression analysis, adjusting for age and gender. Additional adjustment for smoking, atherosclerosis, and the presence of the apolipoprotein E4 allele was performed in separate analyses. To increase the statistical power of the risk analyses, age-related maculopathy stages 1 and 2 were combined, as were stages 3 and 4.

RESULTS

Population at baseline

Age-related maculopathy was absent in 56.4 percent (n = 811) of the study subjects. Of the remaining 627 subjects, 24.3 percent (n = 349) were diagnosed with stage 1, 11.5 percent (n = 165) with stage 2, 3.2 percent (n = 46) with stage 3, and 4.7 percent (n = 67) with stage 4 age-related maculopathy. The baseline characteristics of these subjects are given in table 1. In the more severe stages of age-related maculopathy, sub-
TABLE 1. Baseline characteristics of subjects at risk of incident Alzheimer’s disease, stratified by stage of age-related maculopathy (ARM), the Rotterdam Study, the Netherlands, 1990–1993

<table>
<thead>
<tr>
<th></th>
<th>No ARM (n = 811)</th>
<th>Stage 1 (n = 349)</th>
<th>Stage 2 (n = 165)</th>
<th>Stage 3 (n = 46)</th>
<th>Stage 4 (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline (years) (SD*)</td>
<td>80.5 (4.4)</td>
<td>80.0 (4.0)</td>
<td>81.3 (4.5)</td>
<td>82.2 (5.6)</td>
<td>84.5 (4.8)</td>
</tr>
<tr>
<td>Gender (% women)</td>
<td>64.4</td>
<td>67.9</td>
<td>63.6</td>
<td>67.4</td>
<td>68.7</td>
</tr>
<tr>
<td>Institutionalized (%)</td>
<td>14.8</td>
<td>16.0</td>
<td>21.2</td>
<td>34.8</td>
<td>34.3</td>
</tr>
<tr>
<td>MMSE* score at baseline (SD)</td>
<td>26.9 (2.2)</td>
<td>26.9 (2.1)</td>
<td>26.8 (2.1)</td>
<td>25.5 (4.8)</td>
<td>26.3 (2.5)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>35.6</td>
<td>29.1</td>
<td>33.5</td>
<td>30.2</td>
<td>28.4</td>
</tr>
<tr>
<td>Current</td>
<td>12.1</td>
<td>11.8</td>
<td>13.0</td>
<td>23.3</td>
<td>19.4</td>
</tr>
<tr>
<td>Atherosclerosis (%)</td>
<td>18.3</td>
<td>14.9</td>
<td>22.5</td>
<td>18.6</td>
<td>25.0</td>
</tr>
</tbody>
</table>

* SD, standard deviation; MMSE, Mini-Mental State Examination.

Subjects were older and were more likely to be institutionalized, to smoke, and to have atherosclerosis. There were no significant differences in baseline scores on the Mini-Mental State Examination.

Incidence of Alzheimer’s disease

After an average follow-up period of 25.2 months, 62 incident cases of Alzheimer’s disease were identified. The incidence of Alzheimer’s disease in the total group of study subjects was 20.0 per 1,000 person-years and ranged from 14.0 per 1,000 person-years in those aged 75–84 years to 41.6 per 1,000 person-years in those aged 85 years or older. Figure 1 shows the crude incidence rates of Alzheimer’s disease for successive stages of age-related maculopathy among subjects in two age categories. The 2-year cumulative incidence risks, calculated from the incidence rates, for all subjects aged 75 years or older were 3.4 percent for those with no age-related maculopathy and 3.2 percent for those with stage 1, 3.8 percent for those with stage 2, 9.4 percent for those with stage 3, and 10.0 percent for those with stage 4 age-related maculopathy. Women developed incident Alzheimer’s disease more often than men did, but this difference did not reach statistical significance (relative risk = 1.7, 95 percent confidence interval: 0.9, 3.3; adjusted for age).
Risk of comorbidity

After adjustment for age and gender, we found that the risk of incident Alzheimer's disease increased for subjects with stage 3 or 4 but not for subjects with stage 1 or 2 age-related maculopathy (table 2). After additional adjustment for smoking and atherosclerosis, the point estimate of the relative risk for stage 3 or 4 decreased and the association became insignificant. Additional adjustment for the presence of the apolipoprotein E4 allele did not alter the risk estimates (data not shown).

To investigate whether the association between stage 3 or 4 age-related maculopathy and incident Alzheimer's disease resulted from a decline in visual function rather than age-related maculopathy, we studied the association between poor visual acuity at baseline and incident Alzheimer's disease. For subjects with a best-corrected visual acuity of less than 0.05, the relative risk was 0.96 (95 percent confidence interval: 0.68, 7.05; adjusted for age, age², and gender); for subjects with a best-corrected visual acuity of more than or equal to 0.05 but less than 0.3, the relative risk was 1.01 (95 percent confidence interval: 0.35, 2.88). It is therefore unlikely that the observed association between age-related maculopathy and Alzheimer's disease can be explained by visual impairment.

DISCUSSION

Based on a general population of elderly subjects, this study shows an association between the most severe stages of age-related maculopathy and incident Alzheimer's disease. The nature of this association depends partly on smoking and atherosclerosis, which are important risk factors for both age-related maculopathy and Alzheimer's disease.

Strengths of this study include the setting, methods of diagnosis, and temporal design. The population-based setting warranted a valid comparison of study groups and reduced the possibility of information bias. The standardized methods of diagnosis of both age-related maculopathy and Alzheimer's disease were based on internationally accepted criteria (15, 16), which improved independent case finding. An important part of the design was the temporal sequencing of diagnosis of the two diseases. Poor cognitive functioning of patients with severe Alzheimer's disease generally hampers the performance of extensive clinical investigations, and fundus photography is often difficult to carry out. Therefore, we considered a cross-sectional analysis of the association between age-related maculopathy and Alzheimer's disease to be unreliable. To reduce selection bias, we evaluated the diagnosis of age-related maculopathy prior to the occurrence of Alzheimer's disease. The overall incidence of Alzheimer's disease in the Rotterdam Study was higher than the incidence of this disease in the present study cohort (22), suggesting that subjects for whom age-related maculopathy data were missing were at an increased risk of Alzheimer's disease. Complete data on age-related maculopathy for all subjects would have helped to characterize the actual association. Nevertheless, this does not explain the associations we observed, since the lack of complete data generally tends to weaken any relation.

Both age-related maculopathy and Alzheimer's disease are complex disorders, in which genetic as well as environmental factors have been implicated. Smoking is an established risk factor for age-related maculopathy; the increased risk of incident early or advanced age-related maculopathy has been estimated to be approximately twofold (23-25). Although former studies suggested an inverse relation with Alzheimer's disease (26), it has recently been shown that smoking is also associated with a twofold increased risk of incident Alzheimer's disease (27). In our analysis, smoking partly explains the association between age-related maculopathy and Alzheimer's disease, which may imply that the neurotoxic effect of smoking is rather nonspecific. The exact mechanisms are unknown, but altered hemodynamic and vascular regulation (28, 29) and reduction of oxygen transport into the tissue (30) are some of the destructive effects that may be involved.

Atherosclerosis also partly determines comorbidity of age-related maculopathy and Alzheimer's disease. Earlier findings from the Rotterdam Study suggested that generalized atherosclerosis is a risk factor for either disease; that is, it was associated with a twofold increased prevalence of age-related maculopathy (31) and a 30 percent increased prevalence of Alzheimer's disease (19). Aside from more disease-specific effects such as thickening of Bruch's membrane in age-related maculopathy (32) and increased amyloid angiopathy in Alzheimer's disease (33), decreased vascular flow

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TABLE 2. Relative risk (RR) of incident Alzheimer's disease for subjects with successive stages of age-related maculopathy (ARM), the Rotterdam Study, the Netherlands, 1990–1994

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. at baseline</th>
<th>RR (95% CI)*†</th>
<th>RR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ARM</td>
<td>811</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Stage 1 or 2</td>
<td>514</td>
<td>1.0 (0.6, 1.8)</td>
<td>1.0 (0.6, 1.9)</td>
</tr>
<tr>
<td>Stage 3 or 4</td>
<td>113</td>
<td>2.1 (1.1, 4.3)</td>
<td>1.5 (0.6, 3.5)</td>
</tr>
</tbody>
</table>

* CI, confidence interval.  
† Adjusted for age, age², and gender.  
‡ Adjusted for age, age², gender, smoking, and atherosclerosis.
and endothelial damage are candidate mechanisms by which atherosclerosis may alter both retinal and cortical cell function.

The apolipoprotein E4 allele is associated with both disorders but in an opposite way. The presence of this allele has been shown to increase the risk of Alzheimer’s disease (34, 35) but to decrease the risk of age-related maculopathy (36, 37). It is therefore unlikely that the apolipoprotein E genotype contributes to an association between age-related maculopathy and Alzheimer’s disease. In our analyses, adjustment for the presence of the apolipoprotein E4 allele did not distort the relative risk estimates.

In conclusion, the present study suggests that the neurodegenerative diseases of age-related maculopathy and Alzheimer’s disease show comorbidity and that smoking and atherosclerosis may be causal links. Whether other factors determine a common neurodegenerative pathogenesis remains to be elucidated.

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REFERENCES