Early Age-Related Macular Degeneration, Cognitive Function, and Dementia

The Cardiovascular Health Study

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Objective: To describe the association of cognitive function and dementia with early age-related macular degeneration (AMD) in older individuals.

Methods: This population-based study included 2088 persons aged 69 to 97 years who participated in the Cardiovascular Health Study. The AMD was assessed from retinal photographs based on a modified Wisconsin AMD grading system. Cognitive function was assessed using the Digit Symbol Substitution Test (DSST) and the Modified Mini-Mental State Examination. Participants were also evaluated for dementia using detailed neuropsychological testing.

Results: After controlling for age, sex, race, and study center, persons with low DSST scores (lowest quartile of scores, ≤30) were more likely to have early AMD (odds ratio, 1.38; 95% confidence interval, 1.03-1.85) than were persons with higher DSST scores. In analyses further controlling for education, systolic blood pressure, total cholesterol level, diabetes mellitus, smoking status, and apolipoprotein E genotype, this association was stronger (odds ratio, 2.00; 95% confidence interval, 1.29-3.10). There was no association of low Modified Mini-Mental State Examination scores, dementia, or Alzheimer disease with early AMD.

Conclusions: In this older population, cognitive impairment may share common age-related pathogenesis and risk factors with early AMD.


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In view of these uncertainties and the importance of establishing a relationship, if one exists, we examined the association of cognitive function and dementia with early AMD while controlling for the APOE gene in an older population. Late AMD was not assessed owing to the infrequency of these lesions in the Cardiovascular Health Study (CHS) cohort.

METHODS

STUDY POPULATION

The CHS is a population-based prospective study of coronary heart disease and stroke in adults 65 years and older. Participants were recruited from a random sample of Medicare eligibility lists from 4 US counties (Allegheny County, Pennsylvania; Forsyth County, North Carolina; Sacramento County, California; and Washington County, Maryland). Of the 11,955 participants invited, 3,654 of the sampled individuals and 1,347 age-eligible individuals who lived in the same household as those sampled were recruited after an extensive home visit. In 1992-1993, an additional 687 black individuals were recruited into the study from 3 sites (Forsyth County, Sacramento County, and Pittsburgh) using ethnicity-specific randomized Medicare listings. Differences between those recruited and those not recruited have been presented elsewhere. Informed consent was obtained from all the participants at entry into the study and at periodic intervals. Institutional review board approval was obtained at all sites collecting and analyzing data.

The study population, study design, and methods have been described previously. In brief, 3,888 participants attended the baseline examinations between 1989 and 1993. Of the 4,249 individuals who returned in 1997-1998, retinal photographs were either unavailable or could not be graded in 1,872 individuals. Differences between participants with and without gradable retinal photographs have been previously described.

For this analysis, we additionally excluded 7 individuals for whom cognitive function testing was invalid, 168 who were taking antipsychotic or antidepressant agents at the 1997-1998 visit, and 114 who had a history of stroke before the 1997-1998 visit, which left 2,088 individuals. Comparison of characteristics between participants included (n = 2,088) and excluded (n = 2,161) showed that those included were more likely to be younger and female and were less likely to be black or to have hypertension, coronary heart disease, diabetes mellitus, a history of cigarette smoking, or an education to the level of high school graduate (data not shown).

RETINAL PHOTOGRAPHY AND GRADING

Retinal photography was first offered to participants during the 1997-1998 visit. In brief, the photographs were evaluated for AMD using a modification of the Wisconsin AMD grading system. Grading was performed by the superimposition of a circular grid over the macular area of the retinal photograph, and only lesions detected in the grid area were considered for AMD diagnosis. Early AMD was defined as the presence of soft drusen alone, retinal pigment epithelial depigmentation alone, or a combination of soft drusen with increased retinal pigmen depigmentation in the absence of late AMD. Late AMD was defined as the presence of exudative AMD (subretinal hemorrhage, subretinal fibrous scar, retinal pigment epithelial detachment, or serous detachment of the sensory retina) or pure geographic atrophy. Intragrader and intergrader reliability for most early AMD signs has been assessed previously, with κ values that ranged from 0.67 to 0.81 and from 0.55 to 0.92, respectively. Late AMD was not assessed owing to the infrequency of these lesions.

ASSESSMENT OF COGNITIVE FUNCTION AND DEMENTIA

Participants performed the Digit Symbol Substitution Test (DSST) and the Modified Mini-Mental State Examination (3MSE) during the 10 annual clinic visits between 1989 and 1998. We used the cognitive function data from the 1997-1998 visit concurrent with retinal photography. Assessment of cognitive function and dementia has been described in detail previously. Briefly, the DSST, a subtest of the Wechsler Adult Intelligence Scale, is a measure of psychomotor performance scored as the translation of numbers (1-9) corresponding to novel symbols in 90 seconds, with a maximum score of 93. The 3MSE is a general cognitive battery with components that cover orientation, concentration, language, praxis, and immediate and delayed memory, with a maximum score of 100. Low DSST and low 3MSE were defined as the lowest quartile of the distribution of scores (DSST ≤ 30; 3MSE ≤ 80). We also used an alternative definition using lower than median scores (DSST ≤ 40; 3MSE ≤ 94). In 1998-1999, 3,602 participants were also evaluated for the presence of dementia as part of an ancillary CHS Cognition Study. Dementia was defined as a progressive or static cognitive deficit of sufficient severity to affect the activities of daily living of individuals with a history of normal intellectual function before the onset of cognitive abnormalities. Participants were also required to have impairments in 2 cognitive domains, of which memory may have been one. This definition correlates closely to criteria used in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition). Individuals who did not meet the dementia criteria but who were failing cognitively were classified as having mild cognitive impairment. Dementia was further classified according to subtype and Alzheimer disease using standardized criteria and magnetic resonance imaging.

ASSESSMENT OF GENETIC RISK FACTORS

Genotyping of APOE in the CHS has been previously described. The 3 major allelic forms of the APOE gene (ε2, ε3, and ε4) were determined in the Core Molecular Genetics facility at the University of Vermont College of Medicine, Burlington, using the method of Hixson and Vernier. In statistical analysis, we controlled for APOE status based on 6 common genotypes of APOE.

ASSESSMENT OF VASCULAR RISK FACTORS

Participants underwent an extensive assessment of atherosclerotic disease and its risk factors during the study. Hypertension was defined as a systolic blood pressure of 140 mm Hg or greater, a diastolic blood pressure of 90 mm Hg or greater, or the combination of a self-reported high blood pressure diagnosis and use of antihypertensive medications. Coronary heart disease was ascertained and classified by means of an adjudication process involving medical history, physical examination, and laboratory criteria, including an electrocardiograph. Medical history, medication use, and cigarette smoking status were ascertained from questionnaires. Anthropometry was assessed by measurement of body mass index and waist:hip ratio. Fasting glucose and lipid levels were assessed as previously described. All variables defined were based on the 1997-1998 visit, concurrent with retinal photography and cognitive function assessment, except for data on dementia (1998-1999), blood chemistry (1992-1993), waist:hip ratio (1992-1993), body mass index (1996-1997), and fasting glucose level (1996-1997).
Table 1. Characteristics of Individuals With and Without Age-Related Macular Degeneration (AMD), the 1997-1998 Cardiovascular Health Study Examination

<table>
<thead>
<tr>
<th></th>
<th>Any AMD (n=351)</th>
<th>No AMD (n=1737)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>80.0 (4.7)</td>
<td>78.0 (4.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Women, %</td>
<td>59.0</td>
<td>60.3</td>
<td>.65</td>
</tr>
<tr>
<td>Black, %</td>
<td>8.8</td>
<td>16.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>47.0</td>
<td>48.0</td>
<td>.74</td>
</tr>
<tr>
<td>History of coronary heart disease, %</td>
<td>23.7</td>
<td>22.9</td>
<td>.75</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>131.3 (18.8)</td>
<td>131.7 (19.6)</td>
<td>.72</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>66.2 (10.7)</td>
<td>66.8 (11.1)</td>
<td>.40</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL</td>
<td>199.5 (37.0)</td>
<td>202.9 (39.2)</td>
<td>.14</td>
</tr>
<tr>
<td>LDL cholesterol, mean (SD), mg/dL</td>
<td>125.5 (31.2)</td>
<td>129.1 (32.6)</td>
<td>.06</td>
</tr>
<tr>
<td>HDL cholesterol, mean (SD), mg/dL</td>
<td>53.5 (14.1)</td>
<td>53.4 (13.8)</td>
<td>.88</td>
</tr>
<tr>
<td>Triglyceride, mean (SD), mg/dL</td>
<td>132.3 (72.8)</td>
<td>144.3 (87.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Apolipoprotein E genotype, %</td>
<td>19.6</td>
<td>18.4</td>
<td>.28</td>
</tr>
<tr>
<td>e2 b</td>
<td>62.3</td>
<td>55.6</td>
<td>.37</td>
</tr>
<tr>
<td>e3,3</td>
<td>18.1</td>
<td>17.5</td>
<td>.66</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>16.5</td>
<td>17.5</td>
<td>.93</td>
</tr>
<tr>
<td>Education, completed high school, %</td>
<td>48.6</td>
<td>48.8</td>
<td>.07</td>
</tr>
<tr>
<td>Body mass index, mean (SD)c</td>
<td>26.6 (4.5)</td>
<td>27.1 (4.4)</td>
<td>.15</td>
</tr>
<tr>
<td>Waist-hip ratio, mean (SD)</td>
<td>0.95 (0.08)</td>
<td>0.94 (0.08)</td>
<td>.51</td>
</tr>
<tr>
<td>Cigarette smoking, ever, %</td>
<td>49.3</td>
<td>51.2</td>
<td>.51</td>
</tr>
</tbody>
</table>

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.
SI conversion factors: To convert HDL, LDL, and total cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

*P values relate to analysis of variance, t test (unequal variance), and χ2 test statistics, as appropriate.

b e2 and e4 Carrier genotype.

c Calculated as weight in kilograms divided by height in meters squared.

STATISTICAL ANALYSES

Cognitive function and dementia were the exposure variables, and AMD was the outcome variable. Differences in characteristics between individuals with and without AMD at the 1997-1998 visit were assessed using analysis of variance, the Pearson χ2 test, and the t test for unequal variance, as appropriate. Normality was assessed for all relevant variables, and appropriate nonparametric methods were applied as necessary. Given the nonnormality of the cognitive function scores, their summary statistics are presented as medians (interquartile ranges), and any trend in scores across age groups was assessed using the Cuzick nonparametric test for trend. Logistic regression models were constructed to determine the ORs, 95% CIs, and P values (<.05) for early AMD (vs no AMD) associated with low cognitive function and dementia. In the analyses, we adjusted for age, sex, race, and study center (model 1) and for education (completed high school), systolic blood pressure, total cholesterol level, diabetes, and smoking status (ever smoked) (model 2); a third model was created that included the variables in model 2 and APOE (model 3). Persons with dementia were excluded from the low cognitive function analysis. Cross-product terms were constructed to examine for possible interactions between age, race, sex, hypertension, and diabetes. All analyses were performed using Intercooled Stata 9.2 for Windows (Stata Corp, College Station, Texas).

RESULTS

Of the 2088 participants, any AMD was present in 351 (16.8%); 324 (15.5%) were classified as having early AMD and 27 (1.3%) as having late AMD. Characteristics of persons with and without AMD are given in Table 1. Persons with any AMD were significantly older, were less likely to be black, and were more likely to have a lower triglyceride level compared with those without AMD. There were no significant differences in other characteristics between the 2 groups.

Mean DSST and 3MSE scores decreased with age in persons with and without early AMD (data not shown). Table 2 shows that participants (1760 white, 320 black, and 8 other) with early AMD had lower median DSST and 3MSE scores than did those without AMD; although the difference for the DSST was small (median score of 41 in those without AMD and 39 in those with early AMD), the trend was significant (P < .001). Associations were generally similar for specific early AMD lesions between white and black participants, although they were statistically significant only in whites (data not shown).

After adjustment for age, sex, ethnicity, and study center, persons with low DSST scores (≥30) were more likely to have early AMD (OR, 1.38; 95% CI, 1.03-1.85) than were those with higher scores (Table 3, model 1). This association remained significant after adjustment for the variables in model 1 plus education (completed high school), systolic blood pressure, total cholesterol level, diabetes mellitus, and smoking status (Table 3, model 2) and the APOE genotype (Table 3, model 3). Persons with low 3MSE scores (≤89) were also more likely to have early AMD (OR, 1.21, 95% CI, 0.91-1.62), although this association was not statistically significant (Table 3). Using alternative definitions, in persons with low DSST scores defined using a median DSST score of 40 or less, the findings were similar. A further analysis investigating a 5-point decrease in cognitive function in a 5-year period (measures at the 1992-1993 visit com-
pared with those at the 1997-1998 visit) as a predictor of early AMD in 1997-1998 showed that declines in DSST scores across time, but not in 3MSE scores, were significantly associated with early AMD (Table 4).

Of the 2088 participants, 1672 were evaluated for dementia. Of these, 135 were diagnosed as having dementia, and 86 were classified as having pure Alzheimer disease. There were no statistically significant associations of dementia or Alzheimer disease with early AMD (Table 3). Finally, analyses excluding people with dementia (included n = 1156) showed that the association of DSST score with early AMD persisted (adjusted OR, 2.00; 95% CI, 1.29-3.10; model 3).

**COMMENT**

In this population-based study in an older population, we document the cross-sectional association between low cognitive function and early AMD. After controlling for age, sex, ethnicity, and study center, persons with low DSST scores were more likely to have early AMD. These associations were largely unchanged after further adjustment for education, vascular risk factors, and APOE status. Participants with cognitive test scores in the lowest quartile of the DSST were 2 times more likely to have early AMD signs. While controlling for the same risk factors,
a similar pattern of association was seen for 3MSE scores, although these associations were of borderline nonsignificance. There was no association between dementia and Alzheimer disease, measured by means of detailed neuropsychological testing in the CHS, and early AMD in this population. There were insufficient numbers to assess the associations with late AMD.

Few studies have evaluated the relationship of AMD to cognitive impairment\textsuperscript{25,26} or dementia\textsuperscript{27} for comparison with the present results. In the Atherosclerosis Risk in Communities\textsuperscript{28} population (aged 45-64 years, n=9286), in which an identical protocol to assess AMD signs was used, an association between cognitive impairment, defined as Word Fluency Test scores in the lowest 10% of the population, with early AMD was reported. However, the Atherosclerosis Risk in Communities study found no association between DSST (or Delayed Word Recall) scores and early AMD. The DSST is a sensitive and reliable\textsuperscript{48,49} indicator of neurologic brain damage (although not the location of the abnormality) that is relatively independent of intellectual ability, memory, or learning.\textsuperscript{36} The association with early AMD and low DSST scores found only in the older CHS population suggests a likely shared pathogenesis of AMD and possibly neurologic diseases with increasing age.

The Blue Mountains Eye Study\textsuperscript{20} (3509 participants aged 49-97 years) found an association between cognitive impairment (defined as a Mini-Mental State Examination [MMSE] score <24) and late AMD (OR, 3.7; 95% CI, 1.3-10.6). This association persisted after modifying the MMSE to exclude vision-related items and while adjusting for age, sex, visual impairment, education, and vascular risk factors (OR, 2.2; 95% CI, 1.0-5.0). However, no association was observed between MMSE and early AMD in the Blue Mountains Eye Study. We found a borderline nonsignificant association between low scores on the 3MSE and early AMD.

In the Rotterdam study\textsuperscript{27} (1438 participants aged ≥75 years), the presence of late AMD was associated with a 2-year incidence of Alzheimer disease (age- and sex-adjusted relative risk, 2.1; 95% CI, 1.1-4.3), although this association was attenuated after adjusting for smoking and atherosclerosis (relative risk, 1.5; 95% CI, 0.6-3.5). For early AMD, no association was observed in this study. Consistent with this study, we did not find any association between early AMD and Alzheimer disease. However, we did not have any persons who had both late AMD and dementia or Alzheimer disease for analysis.

The strengths of this study include its large, ethnically diverse, population-based sample; use of standardized and validated methods in assessing cognitive function and AMD; and adjustment for confounders and APOE status. There are several study limitations. First, selection bias, including survival bias, may have affected the observed associations. For example, of the 707 participants evaluated as having dementia in the CHS, only 145 (20.5%) had a gradable retinal photograph and could be assessed for AMD. Moderate to severe dementia generally hampers the performance of clinical investigations such as retinal photography. If persons with AMD were more likely excluded, observed associations would be falsely attenuated, and the results would tend to be biased toward the null. In addition, individuals with AMD and dementia may have died before the CHS Cognition Study, which was 1 year after retinal photography was performed. Furthermore, retinal photography was performed in only 1 eye in the CHS, a factor that would likely have led to an underdetection of AMD.\textsuperscript{25,26} Second, misclassification may have occurred because visual acuity data were not available. The DSST is vision dependent, and the 3MSE contains 4 visuospatial subtests. Participants who could not optimally perform the cognitive function tests might have had visual impairment. This may explain the stronger prospective association of AMD with low DSST scores vs AMD with 3MSE scores, as participants with AMD may have had more difficulty completing the DSST, although vision may not be affected substantially in persons with early AMD. Moreover, the 3MSE was conducted annually, although the words to remember were modified across time. No relationship between

### Table 4. Relationship Between 5-Year Change in Cognitive Function (1992-1993 to 1997-1998) and Early Age-Related Macular Degeneration (AMD)

| Participants | Participants With Early AMD | Model 1 | | Model 2 | | Model 3 | | Model 4 | | Model 5 | |
|--------------|-----------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| No. | (% No.) | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value | Odds Ratio (95% CI) | P Value |
| Decrease in DSST\textsuperscript{1} | 1715 | 286 (16.7) | 1.10 (1.01-1.19) | .02 | 1.10 (1.02-1.20) | .02 | 1.13 (1.03-1.23) | .007 | 1.10 (1.01-1.20) | .02 | 1.11 (1.02-1.22) | .02 |
| Decrease in 3MSE | 1766 | 293 (16.6) | 1.02 (0.93-1.11) | .71 | 1.01 (0.92-1.11) | .78 | 1.05 (0.95-1.15) | .37 | 0.99 (0.90-1.09) | .86 | 0.98 (0.88-1.09) | .71 |

Abbreviations: CI, confidence interval; DSST, Digit Symbol Substitution Test; 3MSE, Modified Mini-Mental State Examination.

\textsuperscript{1}Decrease in DSST and 3MSE scores by 5 points from 1992-1993 to 1997-1998.

\textsuperscript{2}Model 1 was adjusted for age, sex, ethnicity, and study center.

\textsuperscript{3}Model 2 was adjusted for age, sex, ethnicity, study center, education, systolic blood pressure (SBP) (at visit 10), cholesterol level (at visit 9), smoking status (at visit 10), and diabetes (at visit 9).

\textsuperscript{4}Model 3 was adjusted for age, sex, ethnicity, study center, education, SBP (at visit 10), cholesterol level (at visit 9), smoking status (at visit 10), diabetes (at visit 9), and apolipoprotein E (6 genotypes).

\textsuperscript{5}Model 4 was adjusted for age, sex, ethnicity, study center, education, SBP (increase from visit 4 to visit 10), cholesterol level (increase from visit 5 to visit 9), smoking status (change from visit 4 to visit 10), and diabetes (change from visit 4 to visit 9).

\textsuperscript{6}Model 5 was adjusted for age, sex, ethnicity, study center, education, SBP (increase from visit 4 to visit 10), cholesterol level (increase from visit 5 to visit 9), smoking status (change from visit 4 to visit 10), diabetes (change from visit 4 to visit 9), use of antihypertensive medication (visit 10), and family history of heart attack.

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AMD and dementia could be explained by the fact that the CHS Cognition Study adjudication committee took into consideration the effects of poor visual acuity in the participants’ cognitive performance. Third, the definitions of low cognitive function (DSTT score ≤ 30; 3MSE score ≤ 89) may not necessarily be interpreted clinically as overt cognitive dysfunction. However, in the CHS Cognition Study, slightly lower scores on the 3MSE (especially <90) in a short period (1992-1993, 1998-1999) were a predictor of dementia. Finally, this study was cross-sectional. Without temporal information, it is impossible to ascertain whether deterioration of cognitive function occurred before or after AMD.

In conclusion, we found an association between low cognitive function and early AMD in this older population. Persons with cognitive test scores in the lowest quartile on the DSST scale were 2 times more likely to have early AMD signs, independent of vascular risk factors and APOE status. We did not find an association of dementia and Alzheimer disease with early AMD. These data, along with others, provide further support that AMD and cognitive impairment may share similar complex pathogenesis and risk factors.

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Author Contributions: Ms Rogers had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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A full list of participating CHS investigators and institutions can be found at http://www.chs-nhlbi.org.

REFERENCES


27. Wong TY, Hubbard LD, Klein R, et al. Retinal microvascular abnormalities and...

From the Archives of the Archives

This case, which was seen from the first by Alt, is described in the fullest detail and seems to throw a great deal of light as to the manner in which hemorrhages in the retina bring about secondary glaucoma. The eye came to enucleation and was examined carefully in every part, an account of which it is impossible to give here in any detail. The general conclusions, however, which seem to be justified by a careful study of the case are that the disease is primarily one of thrombosis or thrombophlebitis of the larger venous blood-vessels, which leads to rupture of their walls and effusion of blood.

Some of this blood funds its way into the vitreous and is carried by the lymph current of the vitreous to the filtration angle at the base of the iris, causing a plugging up of this space and a consequent obstruction to the exosmosis.

In case the eye is hypermetropic, as it was in the present instance, the filtration angle is small and easily obstructed, and then the condition of glaucoma is readily brought about. Where H is not present or the condition of obstruction of the filtration angle are not so favorable, retinal hemorrhages are not so likely to lead to secondary glaucoma.