Visual Impairment, Age-Related Eye Diseases, and Cognitive Function

The Singapore Malay Eye Study

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Objective: To describe the associations of visual impairment and major age-related eye diseases with cognitive function in an older Asian population.

Methods: A population-based, cross-sectional study of 1179 participants aged 60 to 80 years from the Singapore Malay Eye study was conducted. Visual acuity was measured using the logMAR vision chart. Cataract and age-related macular degeneration were graded using the Wisconsin Cataract Grading System and the Wisconsin Age-Related Maculopathy Grading System, respectively. Glaucoma was diagnosed using the International Society Geographical and Epidemiological Ophthalmology criteria. Diabetic retinopathy was graded using the modified Airlie House classification system. Cognitive dysfunction was defined as a locally validated Abbreviated Mental Test using education-based cutoff scores.

Results: After adjusting for age, sex, education level, income, and type of housing, persons with visual impairment before refractive correction (odds ratio [OR]=2.59; 95% CI, 1.89-3.56) or after refractive correction (OR=1.96; 95% CI, 1.27-3.02) and those with visual impairment due to cataract (OR=2.75; 95% CI, 1.35-5.63) were more likely to have cognitive dysfunction. Only moderate to severe diabetic retinopathy was independently associated with cognitive dysfunction (OR=5.57; 95% CI, 1.56-19.91) after controlling for concurrent age-related eye diseases. No significant independent associations were observed between cataract, age-related macular degeneration, or glaucoma and cognitive dysfunction.

Conclusions: Older persons with visual impairment, particularly those with visual impairment due to cataract, were more likely to have cognitive dysfunction. Furthermore, among the major age-related eye diseases, only diabetic retinopathy was associated with cognitive dysfunction.

Cognitive impairment is an important cause of morbidity in elderly persons, affecting 1 in 4 individuals aged 65 years or older,1 with negative outcomes including functional disability and early mortality.2,3 Visual impairment also affects a large number of elderly adults4 and represents a comorbidity that greatly increases the risk of adverse outcomes in persons with cognitive impairment.5 Some studies have reported associations between reduced visual acuity and poor cognitive function,6-8 but few have investigated the specific vision-threatening eye diseases that may be associated with cognitive impairment. A clearer understanding of these relationships may enhance the development of strategies for reducing the burden of cognitive impairment.

The available evidence on the associations between age-related eye diseases and cognitive impairment remains limited and conflicting. While some studies report that age-related macular degeneration (AMD), diabetic retinopathy (DR), and glaucoma are associated with poorer cognitive test scores and higher prevalence of cognitive dysfunction,9-11 other studies could not confirm these findings.12,13 These inconsistencies may be due to differences in methods, racial/ethnic variations in eye disease prevalence, or underpowered study samples. Prior studies are also limited in not controlling for confounding by concurrent age-related eye diseases, a condition that is prevalent among older adults.
Finally, no studies to our knowledge have examined these relationships in Asian individuals, in whom cognitive impairment is likely to increase substantially in the next few decades with rapidly aging populations.

In view of these uncertainties, we sought to evaluate the following in a general elderly Asian Malay population: (1) the association of visual impairment and cognitive function; and (2) the association of major age-related eye diseases (cataract, AMD, DR, and glaucoma) and cognitive function while controlling for concurrent eye diseases.

METHODS

STUDY POPULATION

The Singapore Malay Eye Study is a population-based, cross-sectional study of 3280 Malay adults aged 40 to 79 years living in Singapore, conducted between August 2004 and June 2006. Study design and population details have been described elsewhere. Only persons aged 60 years and older underwent cognitive screening and were included in this study. Of the 2149 eligible persons aged 60 to 80 years, 1478 participated from 2004 to 2006, yielding an overall participation rate of 76.1%. The response rates by age and sex were 76.3% and 77.2% in men aged 60 to 69 years and 70 to 80 years, respectively, and 78.0% and 72.0% in women aged 60 to 69 years and 70 to 80 years, respectively. We excluded 299 individuals with missing cognitive test data (ie, incomplete or not administered). Excluded persons were more likely to be older, to be diabetic, and to have lower education levels. All study procedures were performed in accordance with the tenets of the Declaration of Helsinki as revised in 1989. Written informed consent was obtained from the subjects, and the study was approved by the institutional review board of the Singapore Eye Research Institute.

ASSESSMENT OF VISUAL IMPAIRMENT

Best-corrected (with refraction corrected by certified study optometrists) and presenting (with participants wearing their glasses or contact lenses, if any) visual acuities (VAs) were measured using the logMAR number chart (Lighthouse International) at a distance of 4 m. If no numbers were read at 4 m, the participants were moved to 3, 2, or 1 m, consecutively. If no numbers were identified, VA was assessed as counting fingers, hand motions, light perception, or no light perception. Visual impairment was defined as greater than 0.30 logMAR in the better-seeing eye (US definition). Visual impairment based on best-corrected rather than presenting VA was used for the main analysis because we wanted to assess the association between vision loss only due to eye diseases (ie, not due to refractive error) and cognitive function, similar to previous studies.

ASSESSMENT OF AGE-RELATED EYE DISEASES

Cataracts were assessed from lens photographs using the Wisconsin Cataract Grading System and defined as nuclear cataract opacity 4 or greater, cortical cataract 25% or greater, posterior subcapsular cataract 5% or greater, or previous cataract surgery. Glaucoma was diagnosed and classified using the International Society Geographical and Epidemiological Ophthalmology scheme based on gonioscopy, optic disc characteristics, and/or visual fields results. The presence of DR was graded from retinal photographs according to a modification of the Airlie House classification system as used in the Early Treatment Diabetic Retinopathy Study. The presence of DR was defined as a severity level of 47 or greater (ie, moderate to severe DR, including proliferative DR that has been treated by laser). The presence of AMD was graded from retinal photographs according to the Wisconsin Age-Related Maculopathy Grading System.

COGNITIVE TESTING

The Abbreviated Mental Test (AMT) is a 10-question test of general cognitive function, derived from the Hodkinson Test. Items assess orientation (3 points), semantic knowledge (1 point), episodic memory (3 points), delayed recall (1 point), picture naming (1 point), and attention (1 point). The AMT was interviewer administered in English or Malay in accord with the participant’s preference to all participants aged 60 years and older. The education-specific cut points for the AMT have previously been validated against the Mini-Mental State Examination. For subjects with 0 to 6 years of education, the optimal cut point was 6 with a sensitivity of 89.6% and a specificity of 92.6%. For subjects with more than 6 years of education, the optimal cut point was 8 with a sensitivity of 82.1% and a specificity of 92.6%. In this study, cognitive dysfunction was defined as an AMT score of 6 or less out of 10 for those with 0 to 6 years of formal education and an AMT score of 8 or less out of 10 for those with more than 6 years of formal education. Persons with vision or hearing difficulties were tested in the same manner and were excluded from the analysis if they were unable to complete the AMT (ie, missing cognitive test data). Persons who had missing data for VA testing (n = 34) were more likely to have cognitive dysfunction than persons who completed the VA test.

ASSESSMENT OF OTHER RISK FACTORS

Participants underwent a standardized interview for socioeconomic measures (eg, income, education, type of housing), lifestyle risk factors (eg, smoking), medication use, and self-reported history of systemic diseases. Fasting venous blood samples were collected for analysis of cholesterol and glucose levels. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or use of antihypertensive medication. Diabetes was defined as a random glucose level of 200 mg/dL (to convert to millimoles per liter, multiply by 0.0559), use of diabetic medication, or a physician’s diagnosis of diabetes.

STATISTICAL ANALYSIS

Age- and sex-adjusted and multivariable-adjusted logistic regression models were used to determine the odds ratios (ORs) and 95% CIs for associations between visual impairment (exposure) or age-related eye diseases (exposure) and cognitive dysfunction (outcome). The potential confounders of dementia were considered were age, sex, glycemic control (hemoglobin A1c level), mean arterial blood pressure, cholesterol level (total, high-density lipoprotein, and low-density lipoprotein), diabetes, hypertension, history of stroke, history of myocardial infarction, smoking status (never smoked, stopped smoking, or current smoker), income category (<SGD $1000, ≥SGD $1000, or retired), type of housing (1- or 2-room government flat, 3- or 4-room government flat, or 5-room government flat or private housing), and education attainment (<6 years of education, completed 6 years of elementary education, or high school or college). Statistically significant confounders were determined using manual backward elimination procedures with a criterion of P > .20 for elimination.
In the analysis between age-related eye diseases and cognitive dysfunction, we further adjusted for the presence or absence of cataract, AMD, DR, or glaucoma (ie, concurrent eye diseases) in addition to confounders not eliminated by the backward stepwise procedure. We then excluded participants with multiple eye diseases and repeated the analysis. Post hoc power analysis was performed using Sample Size Software version 1.0. We also included the cross-product term (sex × visual impairment) in the logistic regression model to evaluate for statistically significant interactions. Because it is unclear how cataract surgery with reversal of visual impairment may affect cognitive function, we further excluded persons with previous cataract surgery in either eye (n = 209) and repeated the analysis.

In a supplementary analysis, the primary causes of visual impairment were assessed by study ophthalmologists on the basis of clinical history, examination, disease definition, and clinical judgment. The associations between the causes of visual impairment and cognitive dysfunction were analyzed in multivariable-adjusted models, using individuals without visual impairment or eye diseases as the reference group. Analyses were performed using Stata version 11 statistical software (StataCorp LP).

RESULTS

We included 1179 subjects (557 women [47.2%]) aged 60 to 80 years from the Singapore Malay Eye Study for analysis. The mean (SD) age was 69.0 (5.5) years, and the mean (SD) best-corrected VA in the better-seeing eye was 0.27 (0.98) logMAR. A comparison of characteristics between persons with and without cognitive dysfunction is shown in Table 1. Persons with cognitive dysfunction were likely to be older and to be female, were less likely to be smokers, had higher cholesterol levels and mean arterial blood pressure, had lower education attainment and income, and had smaller housing types. The AMT score was skewed in the Singapore Malay Eye Study. The median AMT score was 9.0 (interquartile range, 6.0-10.0; full range, 1.0-10.0) in the total cohort, and the age-standardized prevalence of cognitive dysfunction was 30.6% (95% CI, 28.0-33.3).

Based on the best-corrected VA (defined as >0.30 logMAR in the better-seeing eye after correction of refraction), the prevalence of visual impairment was 14.8% (95% CI, 12.8-17.0). Only age, sex, education level, income category, and type of housing were selected by a backward stepwise procedure to be in the multivariable model. Subjects with visual impairment were more likely to have cognitive dysfunction (OR = 1.96; 95% CI, 1.27-3.02) (Table 2). In the analysis based on presenting VA (examined with the subject’s own optical correction, if any), the positive association between visual impairment and cognitive dysfunction was greater (OR = 2.59; 95% CI, 1.89-3.56). We found no statistically significant interactions between sex and visual impairment (P for interaction = .56).

Among the participants, cataract, AMD, DR, and glaucoma were present in 797 (67.6%), 104 (9.8%), 43 (3.9%), and 81 (6.9%), respectively. The associations between age-related eye diseases and cognitive dysfunction are shown in Table 3. Only DR was independently associated with cognitive dysfunction in the multivariable model (OR = 5.57; 95% CI, 1.56-19.91). In analyses excluding cases with multiple eye diseases (n = 133), DR was still significantly associated with cognitive dysfunction (OR = 4.97; 95% CI, 1.38-17.87). Cataract was not significantly associated with an increased risk of cognitive dysfunction. There were also no statistically significant associations observed between AMD and cognitive dysfunction, but the analyses were underpowered. As for the association between glaucoma and cognitive dysfunction, we found no statistically significant association despite having sufficient power (>.80%) to detect the reported effect size. The results remained consistent if persons with previous cataract surgery were excluded (data not shown). We repeated the analysis using a different definition for DR, as a modified Airlie House classification system severity level of 20 or higher in persons with diabetes, simi-
lar to other studies,25,26 and found no significant associations with cognitive dysfunction (data not shown).

In the supplementary analysis, visual impairment as measured by best-corrected VA was attributable to cataract (n=128), AMD (n=2), DR (n=4), glaucoma (n=2), and other ocular conditions (myopic degeneration [n=6], corneal scar [n=2], optic atrophy [n=1], and no obvious cause [n=7]). During the ophthalmic examination in the clinic, a primary cause of visual impairment in each subject was determined by the study ophthalmologists based on the ophthalmologist’s clinical judgment if the subject had more than 1 eye disease. Visual impairment due to cataract significantly increased the risk of cognitive dysfunction after adjusting for age, sex, education, and socioeconomic indicators. In analyses among the age-related eye diseases, we showed that only moderate to severe DR was independently associated with cognitive dysfunction while controlling for other concurrent eye diseases.

Our results showing that poor vision was associated with cognitive dysfunction are in concordance with most studies on older white populations.16,27 The underlying mechanisms are still unclear, although several hypotheses for such an association have been suggested. The common cause hypothesis proposes that age-related changes in a shared factor, such as a general decline in central nervous system function, may confound the association between visual impairment and cognitive dysfunction.28 An alternative hypothesis is that poor vision may be causally associated with factors such as reduced mental and physical activities,29 which are related to an increased risk of cognitive decline.30,31 A number of longitudinal studies showing that baseline poor vision predicts subsequent cognitive decline further suggest that visual impairment may be a risk factor for cognitive dysfunction.6-8

In a community-based population of older Malay persons, individuals with visual impairment due to any causes and, more specifically, due to cataract were more likely to have cognitive dysfunction after controlling for age, sex, education, and socioeconomic indicators. In analyses among the age-related eye diseases, we showed that only moderate to severe DR was independently associated with cognitive dysfunction while controlling for other concurrent eye diseases.

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Our findings of an association between DR and cognitive dysfunction are consistent with earlier findings in the diabetic subgroup of the Atherosclerosis Risk in Communities Study cohort.23 Similarly, a recent study in an elderly cohort with type 2 diabetes showed that poorer

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<th>Table 2. Relationship of Visual Impairment and Cognitive Dysfunction</th>
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Abbreviation: OR, odds ratio.
<sup>a</sup>Adjusted for age and sex.
<sup>b</sup>Includes variables not eliminated by backward stepwise procedure (ie, age, sex, education, income, and type of housing).
<sup>c</sup>Visual impairment is based on best-corrected visual acuity greater than 0.30 logMAR in the better-seeing eye (US definition).
<sup>d</sup>Visual impairment is based on presenting visual acuity greater than 0.30 logMAR in the better-seeing eye (US definition).

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<th>Table 3. Relationship of Age-Related Eye Diseases and Cognitive Dysfunction</th>
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<td>Cognitive Dysfunction, OR (95% CI)</td>
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Abbreviations: AMD, age-related macular degeneration; DR, diabetic retinopathy; OR, odds ratio.
<sup>a</sup>Adjusted for age and sex.
<sup>b</sup>Adjusted for age, sex, education level, income category, and type of housing.
<sup>c</sup>Adjusted for age, sex, education level, income category, type of housing, cataract, AMD, DR, and glaucoma.
cognitive function was found in persons with DR compared with those without DR.10 However, the Cardiovascular Health Study did not find any associations.26 It is noted that both the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study included subjects with mild retinopathy signs (isolated microaneurysms or hemorrhages) in their analysis of relationships between retinopathy and cognitive impairment. In our study, only a moderate or worse level of DR was associated with cognitive dysfunction. More severe DR may correlate with more extensive cerebral and lacunar infarcts, white matter hyperintensities, and cerebral atrophic changes.32,33 These structural magnetic resonance imaging findings have been associated with cognitive dysfunction in diabetic adults.34

Although glaucoma and AMD have been proposed to share common pathogenic mechanisms and vascular risk factors with cognitive impairment,29-33 there is still a lack of data demonstrating relationships between these eye diseases and cognitive function. Data from the few studies available do not demonstrate a consistent association between glaucoma and cognitive impairment,11,12 possibly owing to differing study designs and patient populations. As for the association between AMD and cognitive dysfunction, recent evidence showing a modest association between AMD (especially late AMD) and poorer cognitive test scores provides support for common risk factors or a shared pathogenesis,9,10,37 However, we did not find any significant associations between AMD and cognitive dysfunction, possibly because of insufficient statistical power. There were only 12 cases of late-stage AMD for analysis.

From our supplementary analysis, visual impairment caused by cataract was significantly associated with an increased risk of cognitive dysfunction. In contrast, we did not find statistically significant associations between cataract, irrespective of VA, and cognitive dysfunction. To date, only 1 other study had examined the association between cataract and cognitive dysfunction in a case-control design, and the investigators found no significant association.13 There are several possible explanations for these findings. A greater proportion of persons with cognitive dysfunction may be less likely to seek treatment for cataract even when VA is affected. Another possibility is that severe cataracts or visually disabling cataract subtypes may be markers of underlying etiologic factors (such as systemic oxidative stress) for increased aging and cognitive decline.40-41 The association may also reflect vision loss affecting cognitive decline, but the cross-sectional nature of our study limits determinations of temporality or causality.

Finally, visual impairment based on presenting VA was more likely associated with cognitive dysfunction than visual impairment based on best-corrected VA, which might suggest a role of undercorrected refractive error in cognitive dysfunction. These findings may have important implications because refractive error is a significant cause of visual impairment in the elderly population and is easily corrected.42 Although a previous study on nursing home residents aged 55 years and older did not find improvement in short-term cognitive status after correction of refractive error,43 the benefits of correcting refractive error may warrant further study. Another possibility is that our analyses may have had insufficient sample sizes or selection bias that limited the power, rather than the importance of refractive error, to detect associations between visual impairment and cognitive dysfunction.

Strengths of our study include its large population-based sample, use of a standardized grading protocol for assessing the age-related eye diseases, and detailed assessment of risk factors. We were also able to control for potential confounding by concurrent eye diseases as well as define a reference group with no cataract, AMD, DR, or glaucoma to properly assess associations with cognitive test scores.

Our study should be viewed within the context of its limitations. First, we used the AMT to assess cognitive function. It has been reported that the AMT has lower specificity compared with the Mini-Mental State Examination,44 which could have biased toward a positive association between visual impairment or eye disease and cognitive dysfunction. Furthermore, the AMT score cut points were validated in a group of Chinese rather than Malay adults; interethnic differences might lead to misclassification of cases with abnormal cognitive function. Second, similar to other cognitive screening tests, visual tasks on the AMT (ie, picture naming, time) might put individuals with visual impairment at a disadvantage. If poor vision reduced the accuracy of performance on the AMT, the strength of association between visual impairment and cognitive dysfunction may have been overestimated. In addition, the AMT was administered verbally, which could have affected performance in hearing-impaired subjects. Third, we may have underestimated the association between visual impairment and cognitive dysfunction because persons who were unable to complete the VA test were more likely to have cognitive dysfunction and were excluded from this part of the analysis. Fourth, data on comorbid depression or other confounders that are important risk factors for cognitive impairment were not available and could not be controlled for. Lastly, some analyses were not adequately powered to detect differences.

In conclusion, this study provides population-based data on the associations of visual impairment, specific age-related eye diseases, and cognitive function in elderly Asian Malay individuals. The data show that visual impairment was associated with cognitive dysfunction, independent of age, sex, education, and socioeconomic measures. Of the major age-related eye diseases, only moderate to severe DR may be an independent risk factor for cognitive dysfunction.

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