Age-Related Eye Disease and Cognitive Function

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Purpose. To determine whether people with age-related eye disease have lower cognitive scores than people with healthy vision.

Methods. A hospital-based cross-sectional study was performed in which 420 people aged 65 and older from the ophthalmology clinics at Maisonneuve-Rosemont Hospital (Montreal, Canada) were recruited who had age-related macular degeneration (AMD), Fuch's corneal dystrophy, or glaucoma. Patients with AMD and Fuchs had to have visual acuity in the better eye of worse than 20/40 while patients with glaucoma had to have visual field in their worse eye of at least −4 dB. Controls, recruited from the same clinics, did not have significant vision loss. Cognitive status was measured using the Mini-Mental State Exam Blind Version (range, 0–22) which excludes eight items that rely on vision. Linear regression with bootstrapped standard errors was used to adjust for demographic and medical factors.

Results. People with AMD, Fuch's corneal dystrophy, and glaucoma had lower cognitive scores, on average, than controls ($P < 0.05$). These relationships remained statistically significant after adjusting for factors such as age, sex, race, education, living alone, systemic comorbidities, and lens opacity.

Conclusions. People with vision loss due to three different age-related eye diseases had lower cognitive scores. Reasons for this should be explored using longitudinal studies and a full battery of cognitive tests that do not rely on vision.

Keywords: cognition, AMD, glaucoma, epidemiology

Cognition includes memory, language, orientation, judgment, conducting interpersonal relationships, performing actions (praxis), and problem solving.[1] Several epidemiologic studies have indicated that people with age-related eye diseases like age-related macular degeneration (AMD) or glaucoma have reduced cognitive scores.[2–8] Other studies found a null relationship.[6,9,10] Methodological limitations plagued some of the studies such as not having adequate numbers of people with late-stage AMD, lacking a uniform visual exam for cases and controls, using cognitive tests that require good vision, or limited adjustment for confounding.

In support of the studies that found a positive relationship, there are biological similarities between eye diseases like AMD and glaucoma, and the major cause of dementia, Alzheimer's disease. Some people believe these biological similarities indicate a common pathogenisis. Sivak et al.[11] provide a review of research noting similarities between the three diseases such as retinal damage, amyloid β deposition, pTau, oxidative and metabolic stress, and glial reactivity. Alternatively, instead of a common pathogenesis, it is possible that eye disease leads to cognitive decline via the "use it or lose it" hypothesis of cognitive aging (i.e., when vision is lost at an older age, a person no longer engages in as many physical, cognitive, and social activities, which results in cognitive decline over time).[12]

Given the lack of consistent epidemiologic results on this topic, we examined this issue by recruiting people with one of three diverse age-related eye diseases that differ in which part of the visual system is affected. The three eye diseases that we included were AMD, a retinal disease that affects central vision, glaucoma, a disease of the optic nerve that first affects peripheral vision, and Fuch's corneal dystrophy, a corneal disease that affects both central and peripheral vision. We have included large numbers of people with each eye disease and a control group with healthy vision, everyone had identical vision tests, and we have controlled for numerous confounders. We hypothesized that, consistent with the "use it or lose it" hypothesis of cognitive aging, that all three groups, despite being afflicted with very different eye diseases, would have worse cognitive scores than our control group with healthy vision after adjusting for potential confounders.

Methods

Study Design and Population

All participants were recruited from the ophthalmology clinics of Maisonneuve-Rosemont Hospital in Montreal, Canada between September 2009 and September 2013. Research personnel reviewed patient files each day for five retinal

specialists, five glaucoma specialists, four corneal specialists, and six general ophthalmologists to check for eligible patients who were then approached in the waiting room regarding participation.

To be eligible for the study, participants had to be 65 years or older. Participants had to have either no significant vision loss (controls) or one of three age-related eye diseases clinically diagnosed by a retinal, corneal, or glaucoma specialist: AMD, Fuch's corneal dystrophy, or glaucoma. Each group had to meet certain visual criteria as well because of our hypothesis that when vision is lost at an older age, it will affect the amount of cognitively stimulating activities, which can lead to cognitive decline. The AMD and Fuchs patients were required to have bilateral disease and to have visual acuity of worse than 20/40 in their better eye. Glaucoma patients were required to have bilateral disease and to have a visual field mean deviation worse than or equal to −4 dB in their worse eye. This would be considered "early" visual field loss according to prior literature.[13] All glaucoma types were recruited. The three groups with eye disease were allowed to have other eye diseases, which may have also impaired vision. However, a person was not included if he/she met the visual inclusion criteria for multiple groups (i.e., AMD and Fuchs). Finally, the controls were required to have visual acuity of 20/40 or better in the better eye and a visual field mean deviation in the worse eye better than −4 dB. Controls either had no current eye disease (67%) or they had nonvisually impairing conditions such as early cataract (15%), early AMD (3%), ocular hypertension (5%), blepharitis (3%), or other (e.g., cataract surgery follow-up, pterygium; 6%). People who had received eye surgery, laser, or an intravitreal injection in the last 3 months were enrolled after a 2 to 3 month delay so that their data would be less affected by their treatment and recovery.

There were 776 people who appeared to meet eligibility criteria from a review of the medical records. Of the 776 people, 518 (67%) people accepted our invitation to be in the study, 208 (27%) refused, and 50 (6%) were not capable of responding for themselves. Of the 518 who accepted, 420 people met final eligibility criteria including 113 with AMD, 130 with glaucoma, 66 with Fuch's corneal dystrophy, and 111 people without significant eye disease. Participants were paid $10 for their participation and signed a consent form. The project was approved by the ethics committee of the Hospital and the research conformed to the tenets of the Declaration of Helsinki.

Data Collection

Data were collected from questionnaires, vision tests, and a review of the medical record, in that order. Cognitive status was measured using the Mini-Mental State Exam (MMSE) Blind Version, which was validated by Busse et al.[14] The Blind Version omits eight items that directly or indirectly rely on vision. The MMSE Blind Version is a global test of cognition. Participants with scores less than 17 meet the criteria for cognitive impairment.[14] Demographic information was collected on age, sex, ethnicity, and highest grade of education. Participants were asked if they lived alone and about the presence or absence of a physician diagnosis of 13 chronic conditions such as diabetes, heart disease, arthritis, and so on.

Visual acuity was tested using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart with illuminated light box at 2 or 1 m if the participant could not read any letters at 2 m.[15,16] Letter by letter scoring was performed with scores at 2 m converted to scores at 1 m by adding 15. Scores were converted to logMAR. Contrast sensitivity was measured using the Pelli-Robson chart at 1 m for each eye.[17] Forced choice letter-by-letter scoring procedures were used until a participant read all three letters of a triplet incorrectly. Visual field was measured using the Humphrey frequency doubling technology (FDT) test with full threshold N-30 testing in each eye.[18] The FDT measures 30° horizontally and 24° vertically.

The medical record was reviewed and further detail on the patient's eye disease and any coexisting eye disease (such as lens opacity) was recorded. Those who could not obtain a reliable result on the FDT test (15%) had their last visual field exam results taken from the medical record.

Statistical Analysis

The primary outcome was the continuous score from the MMSE Blind test. The mean MMSE Blind scores were compared between the four groups (AMD, Fuchs, glaucoma, control) by the ANOVA test. Multiple linear regression was used to determine whether the groups with eye disease had worse cognitive scores adjusting for demographic and health factors that were considered potential confounders. Given the skewed MMSE Blind distribution, standard errors and 95% confidence intervals (CI) for the regression coefficient estimates were obtained from bootstrapping (2000 replicates).[19] Analyses were done in Stata Version 11.0 (College Station, TX, USA).

Results

We enrolled 420 people who resided in the community (82%), assisted living facilities (8%), and retirement homes (10%). Characteristics of the four groups are shown in Table 1. The groups with age-related eye disease were older, had less education, and had more systemic comorbidities than the control group ($P < 0.05$). The AMD and Fuchs groups had a greater percentage of women than the control group ($P < 0.05$). The mean visual acuity of the AMD and Fuchs groups was 20/100 and 20/80, respectively. The average visual field mean deviation in the better eye in the glaucoma group was −9.5 dB. The mean MMSE Blind scores were lower in the three groups with age-related eye disease than in the control group ($P < 0.001$). Also, a greater percentage of people in the groups with eye disease had cognitive impairment compared with the control group ($P = 0.019$).

After adjustment for demographic and health factors (Table 2), all three groups with age-related eye disease had lower MMSE Blind scores than the control group ($P < 0.05$). Scores were between 0.7 and 0.8 units lower than the control group, on average. Other factors that were associated with worse cognition included older age and African descent ($P < 0.05$). Better education and living alone were associated with better cognition ($P < 0.01$).

In sensitivity analyses, we further adjusted the model in Table 2 for depression despite some concern that it could be a mediator of the relationship between eye disease and cognition (i.e., in the causal pathway).[20] All three eye diseases remained statistically significantly associated with cognitive status although the results were somewhat attenuated (data not shown). In other analyses, adding either contrast sensitivity, visual field, or visual acuity to the model in Table 2 resulted in none of the eye-disease variables being statistically significant.

In Table 3, we removed the eye-disease variables and instead examined which measures of visual function were most strongly related to cognitive function. In separate models, contrast sensitivity and visual acuity were highly statistically significant ($P < 0.001$) while visual field in the better eye had borderline statistical significance ($P = 0.09$). The placement of all three measures of visual function in the model together results in none of them being statistically significant due to the

Table 1. Description of the Eye Disease and Control Groups

	AMD Mean (SD) or % $n = 113$	Fuch's Mean (SD) or % $n = 66$	Glaucoma Mean (SD) or % $n = 130$	Controls Mean (SD) or % $n = 111$	*P* Value*
Age	82.5 (6.4)	78.5 (7.1)	76.6 (7.6)	74.0 (4.9)	<0.001
Female sex	75%	83%	58%	59%	<0.001
Ethnicity					
Caucasian	100%	100%	89%	97%	0.001
African descent	0%	0%	11%	3%	
Education, y	9.4 (3.4)	10.9 (4.5)	10.9 (4.2)	11.8 (3.7)	0.001
Binocular visual acuity, logMAR	0.71 (0.40)	0.59 (0.31)	0.27 (0.29)	0.04 (0.06)	<0.001
Log contrast sensitivity in better eye, letters correct	1.09 (0.41)	1.16 (0.34)	1.29 (0.34)	1.80 (0.15)	<0.001
Visual field in better eye, MD, dB	−3.1 (3.7)	−2.9 (3.6)	−9.5 (6.6)	0.5 (2.0)	<0.001
Lens opacity	29%	26%	28%	15%	0.057
MMSE Blind Version (max 22)	19.1 (2.6)	19.7 (2.6)	19.3 (2.9)	20.7 (1.4)	<0.001
Cognitive impairment	14%	14%	12%	3%	0.007
Number of comorbidities	3.3 (1.9)	2.9 (1.9)	2.6 (1.6)	2.0 (1.5)	<0.001
Live alone					
Yes	53%	41%	32%	39%	0.008
No	47%	59%	68%	61%	

* *P* value derived from ANOVA for continuous variables or χ^2 test/Fishers exact test for categorical variables. MMSE, Mini-Mental State Exam.

colinearity of logMAR visual acuity and contrast sensitivity (Pearson's $r = -0.78$).

Discussion

Consistent with our hypothesis, all three of the groups with age-related eye disease had lower cognitive scores when compared with the control group. This is despite the fact that the three diseases all affect different parts of the eye, leading one to believe that the relationships may not primarily be due to common pathogenesis.[11] An alternative explanation is that these relationships are due to the "use it or lose it" hypothesis of cognitive aging (i.e., the loss of vision at an older age leads to a lack of physical, cognitive, and social stimulation that over time is harmful to the brain).[12]

There is a lot of cross-sectional and longitudinal support for the "use it or lose it" hypothesis of cognitive aging, also known as the engagement hypothesis. For example, numerous observational studies have shown that participation in cognitively stimulating activities decreases the risk of cognitive impairment.[21–25] Furthermore, randomized clinical trials have found that cognitive training programs can improve cognitive function.[26,27]

One of the proposed mechanisms to explain the "use it or lose it" hypothesis is via an active cognitive reserve in which a person's environment (lifelong activities, occupation, and education) affects neural processing and synaptic organization, thereby causing neurological processes to become more efficient, adaptive, and plastic.[12,28] Therefore, a greater active cognitive reserve could compensate for brain pathology up to a certain threshold. Physiological changes accounting for this active cognitive reserve are not known for certain but may include changes to cerebral blood flow, the number of synapses in the brain, or more optimal neurochemical compositions.[12,28]

People who lose vision at an older age may have difficulty doing visually intensive cognitive activities that they enjoyed before they lost their vision (e.g., reading, driving, knitting, cooking, etc). Studies have in fact found that older adults with lower levels of visual acuity have reduced levels of leisure-time activities.[29,30] This could over time lead to the loss of an active cognitive reserve and a diminished cognitive performance. It may be possible to reverse or prevent this process in people with vision loss. However, cognitive training programs that have shown efficacy in clinical trials excluded people with poor vision because of the visually intensive nature of the intervention.[26]

Our results showing that glaucoma and Fuch's corneal dystrophy are related to reduced scores on the MMSE Blind version are novel, to our knowledge. In support of this, some studies have found higher rates of glaucoma in people with Alzheimer's disease.[7,8] Other studies have not found a link between glaucoma and Alzheimer's disease or cognitive function.[6,9,10] Our results confirm findings from the Blue Mountains Eye Study, which also found that people with late AMD had lower scores on the MMSE minus five items that relied on vision (the MMSE Blind Version that we used omits 8 items).[4] People with AMD have also had worse scores on other cognitive tests.[2,3]

Table 2. Relationships Between Age-Related Eye Disease and Cognitive Status From a Multiple Linear Regression Model

Multiple Linear Regression Model	Cognition β	Bootstrapped 95% CI
Eye Disease Group		
Control	0.00	
AMD	−0.81	−1.44, −0.19
Fuch's	−0.82	−1.53, −0.12
Glaucoma	−0.72	−1.21, −0.19
Age	−0.06	−0.09, −0.03
Sex		
Male	0.00	
Female	0.46	−0.05, 0.99
Ethnicity		
Caucasian	0.00	
African descent	−2.25	−3.84, −0.79
Education	0.21	0.14, 0.27
Live alone	0.61	0.19, 1.05
Number of comorbidities	−0.00	−0.13, 0.14
Lens opacity	0.10	−0.46, 0.60

Table 3. Multiple Linear Regression Models Showing Adjusted Relationship Between Three Measures of Visual Function and Cognitive Status

		Cognitive Status	
Model	Visual Function Variable	β	Bootstrapped 95% CI
Model 1*	Binocular Logmar acuity, per 0.1 unit	−0.11	−0.18, −0.04
Model 2*	Log contrast sensitivity, per 0.1 unit	1.40	0.72, 2.13
Model 3*	Visual field in better eye, per 1 dB	0.04	−0.003, 0.08

* All models also adjusted for age, sex, ethnicity, education, number of comorobidities, living alone, and lens opacity.

The three groups, despite having very different profiles of vision loss, were approximately equally affected, on average, as the mean MMSE scores of the groups with eye disease were 0.7 to 0.8 points lower than the controls, a modest difference. The MMSE is a global cognitive test that was designed to detect cognitive impairment. When used as a continuous measure, it suffers from a ceiling effect (i.e., compression of scores at the top end of the distribution) when used in populations who are relatively free of cognitive impairment. Future studies should use a variety of cognitive tests appropriate for people with limited vision that evaluate different domains of cognition and that can finely differentiate cognitive ability even at the top end of the range. For example, some cognitive tests that do not rely on vision and do not suffer from a ceiling effect include the verbal digit span test, the 18-item story with immediate and delayed recall, and the 1-minute verbal fluency test.[31–33] Furthermore, longitudinal studies are essential to examine the temporality of the vision loss, activity limitation, and cognitive decline given the evidence of a dynamic, bidirectional association between activity levels and cognition.[34]

A strength of this study is that we had relatively large numbers of people with eye disease compared with the population-based studies that have previously been done. Furthermore, our controls were recruited from the same clinics as the people with eye disease, which helps to ensure their similarity and to guard against bias. In fact, the mean full scale MMSE score in our controls was 28 (SD = 1.6), which is identical to people of a similar age in population-based studies.[35] We used a validated cognitive test that omitted eight items that directly or indirectly rely on vision (MMSE Blind Version).

This study also has some limitations. Our data are cross-sectional, which precludes our ability to determine whether vision loss preceded cognitive decline or vice versa. We only had a single, global cognitive test rather than a variety of cognitive tests that measure different domains of cognition. We do not have data on certain potentially important confounders like smoking, diet, genetic factors, and atherosclerosis. Future studies should include these factors. We were unable to obtain a reliable FDT test on 15% of the sample and therefore used data from the last recorded mean deviation in the medical chart. Almost all of these individuals were in the glaucoma group and had very poor vision. Finally, a 67% response rate is quite good for a clinical study. However, it is possible that those who did not participate have biased our results. Those who refused were 3-years older on average than those who participated and those who were unable to participate were 5-years older on average ($P < 0.001$). Those who refused or were unable to participate were more likely to be male than those who participated ($P = 0.03$).

Reasons why age-related eye disease and cognitive decline are related need further investigation. Cognitive decline is a major risk factor for admission to nursing home facilities and a great cost to society,[36,37] and on top of visual impairment, is doubly disabling. Efforts to better understand and prevent cognitive decline in people with poor vision are necessary.

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