Cognitive Dysfunction and the 25-Item National Eye Institute Visual Function Questionnaire

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Abstract

Research Question:
Do elderly individuals (ages 65 and above) with cognitive dysfunction have decreased self-reported visual function (quantified by overall National Eye Institute's Visual Function Questionnaire (NEI VFQ) composite score) compared to elderly individuals with normal cognition?

The goal of this study is to characterize the relationship between cognition (based on Mini-Mental State Examination score (MMSE)) and self-reported visual function (based on NEI VFQ-25 score), and to examine the relationship between clinical neuropsychological diagnosis (i.e., normal cognition, mild cognitive impairment, Alzheimer's disease) and self-reported visual function.

Background, Significance, and Rationale for the Question:
Cognitive dysfunction and visual impairment often coexist in the elderly population. Decreased visual function is a significant burden for these individuals and can lead to disability and decreased quality of life. Furthermore, visual impairment is associated with an increased risk of Alzheimer's disease (AD) as well as an increased clinical severity of AD. Although visual function and cognitive impairment are interrelated, little is known about the impact of modifying treatable vision impairment on the development and progression of cognitive dysfunction. This study examines the relationship between cognition and self-reported visual function using the National Eye Institute's Visual Function Questionnaire (NEI VFQ).

Materials and Methods:
The research cohort was recruited from the Alzheimer's Disease in Primary Care (ADPC) study at UNTHSC. The participants completed the Mini-Mental State Examination (MMSE) for assessment of cognition, as well as the National Eye Institute's Visual Function Questionnaire (NEI VFQ) to assess self-reported visual function. Additionally, as a part of the ongoing ADPC study, participants underwent rigorous neuropsychological testing and were assigned a clinical consensus diagnosis based on established criteria. Statistical analyses of the data included a general linear model and an analysis of variance approach to compare means between multiple groups.

Results:
The data revealed a statistically significant association between overall composite score on the NEI VFQ and the total MMSE score ($P = 0.04$). On average, for every 1-point increase in MMSE score, the overall composite NEI VFQ score increased by 0.40 units (95% confidence interval: 0.03 – 0.77).

Conclusions:
Reduced visual function should raise concern for cognitive decline and prompt additional assessment. Implementation of screening tools such as the NEI VFQ could help to identify modifiable causes of visual impairment and thus have the potential to impact cognition.

Research Question

Do elderly individuals (ages 65 and above) with cognitive dysfunction have decreased self-reported visual function (quantified by overall NEI VFQ composite score) compared to elderly individuals with normal cognition?

The goal of this study is to characterize the relationship between cognition (based on MMSE score) and self-reported visual function (based on NEI VFQ-25 score), and to examine the relationship between clinical neuropsychological diagnosis (i.e., normal cognition, MCI, AD) and self-reported visual function.

Introduction, Significance, and Rationale

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that causes cognitive dysfunction, including impairments in memory, thinking, and communication. AD is the most common cause of dementia and predominantly affects individuals who are 65 years and older.[1] Patients with AD often have concomitant visual deficits. Specifically, AD pathology can be found in both the central and peripheral visual systems of AD patients.[2] Visual dysfunction in AD patients is correlated with structural changes within the retina.[3] Importantly, even in AD patients who lack visual impairment, a reduced retinal thickness and diminished retinal vasculature have been demonstrated compared to control patients.[4,5] Ocular comorbidities related to AD have been widely studied. However, the impact of cognitive dysfunction on visual function in such patients has not been elucidated.

Cognitive dysfunction can be viewed as a spectrum in which normal cognitive function is at one end, and the dementia experienced by AD patients is at the other end. Mild Cognitive Impairment (MCI) is a series of cognitive changes between these two ends of the spectrum. It involves some memory loss, although patients with MCI are still able to perform activities of daily living. MCI is the symptomatic predementia phase of AD, and often does progress to AD.[6] The clinical course of AD can be characterized as follows: first, a prodromal phase in which pathology accumulates without symptoms; second, an early clinical phase in which cognitive dysfunction and memory loss manifest (once pathology and neuronal injury have reached a certain threshold); and third, a later clinical phase in which there is more severe cognitive dysfunction and functional decline.[7] Understanding the progression of cognitive dysfunction from normal to AD is important when evaluating and comparing metrics such as visual function among individual patients.

The interplay between cognition and visual function in patients across the spectrum of cognitive dysfunction (including normal, MCI, and AD) is the primary interest of this research study. Visual impairment is associated with both an increased risk of AD as well as an increased clinical severity of AD.[8] Recent studies have shown a correlation between age-related eye diseases, including macular degeneration, diabetic

retinopathy, and glaucoma, and the risk of developing AD.[9] However, it is not clear whether the visual impairment causes the dementia or whether it is a marker of disease severity.[10] It has been shown that visual impairment predicts cognitive dysfunction in AD and that visual impairment in AD may also functionally impact the performance of certain cognitive domains.[11] This study aims to more clearly understand the influence of visual function on cognitive function, and vice versa.

Self-reported visual function was assessed in patients via the 25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The advantage of this vision test is that it is designed to capture the impact of visual disability on multiple dimensions of health-related quality of life (HRQOL), including physical functioning, emotional well-being, and social functioning. The questionnaire is specific for individuals with vision problems, but it is not designed for any one specific ocular disease.[12] Thus, it can be used to assess the effect of a range of vision-related issues in research participants engaged in this clinical study.

Lastly, this study will utilize the Mini-Mental Status Examination (MMSE) in order to evaluate cognitive dysfunction in study participants. The MMSE is useful in screening for dementia in clinical settings, as well as many other neurologic and psychiatric disorders.[13] The examination is a measure of global cognition and is helpful in estimating the severity of cognitive dysfunction in patients.

Significance

There are currently more than 5 million Americans that are living with Alzheimer's disease. AD is a progressive disease which can become so severe that it limits a person's ability to perform activities of daily living. The majority of people with AD are 65 years or older. While there are medications that help manage the symptoms and slow the disease course, there are currently no disease-modifying treatments that can cure AD. The personal cost of AD for a patient and their loved ones is immense. And, as the 6th leading cause of death in the United States, AD is also a significant public health concern.[1]

By 2030, 1 in 5 Americans are projected to be age 65 or older.[14] This demographic shift is expected to be accompanied by an increased prevalence in chronic, age-related diseases, including AD. This will intensify demands on the health care system, as well as increase the need for additional caretakers and facilities to help AD patients that can no longer take care of themselves. All of these factors will contribute to soaring health care costs and the expanding economic burden of this disease.

Rationale

AD is associated with visual impairments that can have a profound impact on an individual's autonomy in everyday life. Ocular diseases can be disabling, and thus can affect health-related quality of life. Tests of visual acuity do not fully encompass the impact of visual dysfunction on the lives of AD patients. Thus, this study will employ the

use of the NEI VFQ-25 in order to understand the impact of visual disability on multiple dimensions of HRQOL and to test the utility of the questionnaire as an additional tool in addressing vision-related problems that are associated with AD, especially in the primary care setting.

The interconnected relationship between cognitive dysfunction and visual impairment suggests that VI is a potential risk factor that, if identified and treated early, could improve AD prognosis and HRQOL. Given that 80% of the etiologies of VI can be treated or cured, the development of effective vision screening tools in the elderly population is essential in identifying those treatable vision problems.[15] Identifying modifiable risk factors for cognitive impairment and treating them allows the opportunity to improve HRQOL for individuals with dementia.

Although specialized neurodiagnostic procedures are available for AD, including CSF analysis and PET scans, the detection of AD is poor in primary care settings.[16] This study will leverage the infrastructure of the ongoing Alzheimer's Disease in Primary Care (ADPC) study, which is examining blood-based biomarkers for AD among primary care patients, in order to delineate the connection between cognitive dysfunction and visual dysfunction. Specifically, the aim of this study is to characterize the relationship between cognitive dysfunction (based on MMSE score) and self-reported visual function (based on NEI VFQ-25 score), and to compare the level of visual function (as self-reported on the NEI VFQ-25) to patients' clinical neuropsychological diagnosis (i.e., normal cognition, MCI, AD).

The long-term goal is to validate and include ocular biomarkers as components of the multi-faceted neurodiagnostic algorithm for AD. Furthermore, the identification of visual dysfunction in patients, regardless of their level of cognitive dysfunction, provides an opportunity to address those deficits via optical correction, low-vision devices, or disease therapy. These interventions have the potential to reduce the risk of visual disability and improve the HRQOL in patients with AD, thus decreasing individual and societal burden of the disease.

Research Materials and Methods

Alzheimer's Disease in Primary Care (ADPC) Study

The ADPC study is an ongoing research investigation (R01AG058537) at the University of North Texas Health Science Center (UNTHSC). It is the first-ever examination of blood-based biomarkers for AD among primary care patients. The study involves a patient interview, an informant interview, neuropsychological testing, medical examination, blood draw, brain MRI, and brain amyloid PET scan for each participant.

As part of our ancillary study, the NEI VFQ-25 will be added as a supplement to the series of ADPC study tests for each participant.

Resources and Research Environment

I am working under the supervision and guidance of my research mentor, Dr. Sima Mozdbar, who is an assistant professor in the Department of Pharmacology and Neuroscience at UNTHSC. Dr. Sid O'Bryant and Dr. Leigh Johnson, affiliated with the Institute for Translational Research (ITR) at UNTHSC, are the principal investigators for the ADPC study. Dr. Subhash Aryal, a former associate professor in the Department of Biostatistics and Epidemiology at the UNTHSC School of Public Health, is the statistical collaborator for the project.

Dr. Mozdbar developed the Ophthalmic Clinical Research Center on the UNTHSC campus. It is located within the Institute for Translational Research, where the ADPC study is being conducted, and contains four rooms (two testing rooms and two examination lanes).

Patient Recruitment

Patients for the ADPC study are recruited from the UNTHSC Department of Family Medicine clinics and local primary care offices. Since 2013, Dr. O'Bryant has recruited more than 8,000 older adults into clinical and community-based studies. The current study is recruiting up to 200 patients that have been referred from primary care settings.

Participants must be age 65 or older and have a memory complaint (from themselves or a third party such as a relative or primary care provider). In order to be included in the study, patients must have an available and reliable informant to discuss the patient's activities of daily living. They must be willing to undergo clinical dementia AD examination and venipuncture. Additionally, patients must be capable of undergoing MRI and amyloid PET scans.

Potential participants were excluded from the study based on the following criteria: presence of current cancer or current uncontrolled inflammatory condition (e.g., urinary tract infection) at the time of blood draw, current or recent cancer (in the previous 12 months), current active psychiatric condition that could impact cognition, current use of medications that could impact cognition (e.g., anticonvulsants, benzodiazepines, narcotics, sedative-hypnotics), recent traumatic brain injury with loss of consciousness (in the previous 12 months), current or recent alcohol or substance abuse, and active severe medical condition that could impact cognition (e.g., CKD/ESRD, dialysis, CHF, COPD).

This study recruited 131 participants from the ADPC research cohort to complete the NEI VFQ.

25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25)

The NEI VFQ-25 was added as a supplement to the ADPC study. The questionnaire was administered in English or Spanish (based on participant preference) on an iPad tablet within the ophthalmic clinic at the Institute for Translational Research at UNTHSC. The NEI VFQ-25 consists of 25 questions that fall within 12 subscales that measure the impact of ocular disease on multiple domains of health, including: general health, general vision, near vision, distance vision, driving, peripheral vision, color vision, ocular pain, vision-specific role limitations, dependency, social function, and mental health.[12] Additionally, participants were asked to report whether they have ever been diagnosed with an eye disease or condition. Each subscale is scored so that 0 is the lowest possible score (low visual function/low vision-related quality of life) and 100 is the highest possible score (high visual function/high vision-related quality of life). For participants who do not drive, the driving subscale was excluded from the overall score.[12] The overall composite score is calculated by performing an unweighted average of the answers to all of the individual questions, excluding the general health rating question. The composite score provides an overall measure of vision-targeted HRQOL. The general health rating question is an isolated measure that serves as a robust indicator of future health and mortality. It is valuable as a comparative benchmark in longitudinal analyses. The goal of implementing the short-form version of the NEI VFQ is to maintain reliability and validity of the survey, while increasing time efficiency of its administration – it can be completed in approximately 5 minutes.[12]

Clinical Dementia Examination and Diagnosis

The clinical examination includes a patient interview, neuropsychological testing, medical examination, and 3T MRI of the brain. The neuropsychological testing is extensive, and it assesses all cognitive domains. For the purposes of the current study, the Mini-Mental Status Examination (MMSE) scores were used to assess global cognitive function. The MMSE is useful in screening for dementia, as well as many other neurologic and psychiatric disorders. It is scored from 0 to 30, with 30 representing the best level of cognitive function and scores below 24 indicating cognitive impairment.[13,17]

All patient information was reviewed by a consensus panel that includes medical personnel, a neuropsychologist, study coordinator, and interviewers. Clinical consensus diagnoses were assigned algorithmically based on the neuropsychological tests and results of the informant interview for completion of the Clinical Dementia Rating scale (CDR). This was verified at consensus review as follows:

- Normal Control (NC) – no cognitive complaints, CDR Sum of Boxes (CDR-SB) score of 0[18,19] and cognitive test scores broadly within normal limits (i.e., performance greater than that defined as meeting diagnostic criteria for mild cognitive impairment
- Mild Cognitive Impairment (MCI) – cognitive complaint (self or other), CDR-SB score between 0.5 and 2.0 and at least one cognitive test score falling ≤ 1.5 standard deviations below normative ranges

- Alzheimer's Disease Dementia (AD) – CDR-SB score ≥ 2.5 and at least two cognitive test scores 2 standard deviations below normative ranges

The final clinical diagnosis of AD was assigned according to the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria, and MCI, the symptomatic predementia phase of AD, was assigned according to the appropriate NIA-AA criteria as well.[20,21] Biomarker-based assignments utilizing PET amyloid results are ongoing.

Statistical Analysis

The goal of this study is to characterize the relationship between cognition (based on MMSE score) and self-reported visual function (based on NEI VFQ-25 score), and to examine the relationship between clinical neuropsychological diagnosis (i.e., normal cognition, MCI, AD) and self-reported visual function.

We obtained the mean and standard deviation for continuous variables and the frequency distributions for categorical variables. Histograms and boxplots were used as graphical approaches to evaluate the normal distribution assumption. The primary outcome variable was overall composite score calculated as the mean of 12 subscales of the NEI VFQ. This was analyzed as a continuous variable outcome. The primary predictor variable was clinical classification (normal, MCI, or AD). This was included as a categorical grouping variable. Due to the link between age-related ocular diseases and cognitive impairment,[9] disease classification was also used as a predictor variable. Disease classification was defined as no glaucoma, cataract, or age-related macular degeneration (AMD); glaucoma only; cataract only; AMD only; and two or more conditions. This was included as a categorical grouping variable. Similarly, the MMSE score was analyzed as a continuous outcome variable using a linear regression model. Diabetic retinopathy and diabetic macular edema were not included as predictors because none of the participants reported having these conditions.

A general linear model and an analysis of variance approach was utilized to compare means by clinical classification and disease classification for normally distributed outcomes. For non-normal distributions, a Kruskal-Wallis test was used. A logistic regression model was used for analysis that involved binary outcome variables. Additional covariates in the model included age, sex, race, education, and self-reported ocular disease. Age was reported in number of years and education level was reported as the number of years attending school. Both of these were included as continuous variables in the analysis. Sex was categorized as female or male. This was included as a binary categorical variable. Lastly, race (four categories), disease classification (five categories), and clinical classification (three categories) were included as categorical covariates in the model. The type I error rate was set a priori at $\alpha = 0.05$.

Results

Descriptive Statistics

This study recruited 131 ADPC participants to complete the NEI VFQ as part of the interview. All individuals were aged 60 or older, with a mean participant age of 71.63 years (standard deviation = 5.51). The sample consisted of 84 (64.1%) females and 47 (35.9%) males. In terms of clinical classification, 80 (61.1%) of the participants had normal cognition, 35 (26.7%) were diagnosed with MCI, and 16 (12.2%) were diagnosed with clinical AD. Descriptive statistics for the participants can be found in Table 1.

TABLE 1 Descriptive statistics for overall sample

Variable	*n* (%)
Sex	
Female	84 (64.12%)
Male	47 (35.88%)
Race	
Non-Hispanic White	97 (74.05%)
Hispanic	12 (9.16%)
Asian	3 (2.29%)
Black/African American	19 (14.50%)
Disease classification	
No glaucoma, cataract, AMD	79 (60.31%)
Glaucoma	4 (3.05%)
Cataract	37 (28.24%)
Age-related macular degeneration	5 (3.82%)
2 or more	6 (4.58%)
Clinical classification	
Pre-clinical or normal	80 (61.07%)
Mild cognitive impairment	35 (26.72%)
Dementia	16 (12.21%)
Age	
	Mean (SD)
	71.63 (5.51)

Abbreviation: AMD, age-related macular degeneration.

Table 1

Linear Regression Model

Data analysis revealed a statistically significant association between participants' overall composite score on the NEI VFQ and their total MMSE score (P = 0.04). On average, for every 1-point increase in MMSE score, the overall composite NEI VFQ score increased by 0.40 units (95% confidence interval [CI]: 0.0266–0.7718). This association remained significant in an adjusted model (P = 0.01), which included sex, age, race, and education as covariates. On average, after adjusting for sex, age, race, and education, for every 1-point increase in MMSE score, the overall composite NEI VFQ score increased by 0.60 units (95% CI: 0.1333–1.0796). The linear regression plot of total MMSE score and NEI VFQ overall composite score can be found in Figure 1.

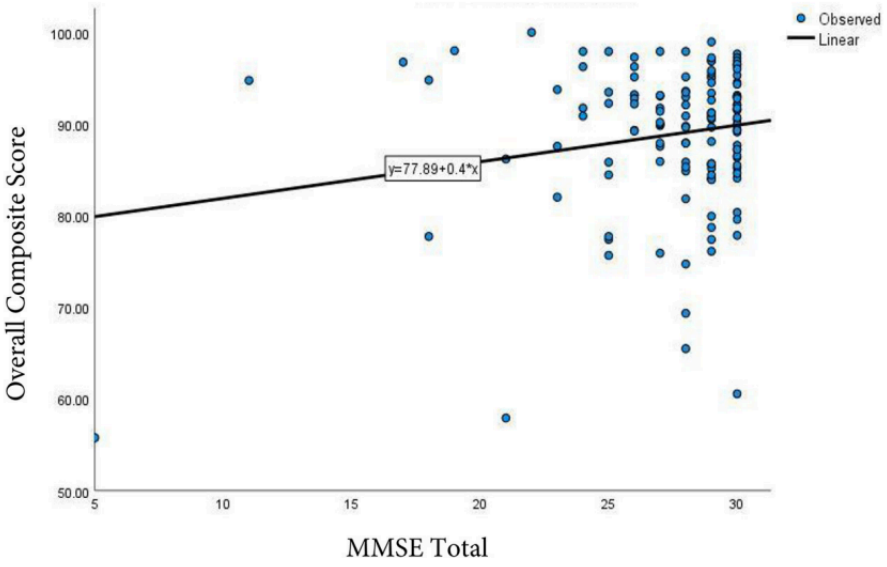

FIGURE 1 The overall composite score on the NEI VFQ 25 and total MMSE score (unadjusted analysis). NEI VFQ-25, National Eye Institute 25-Item Visual Function Questionnaire; MMSE, Mini-Mental State Examination

Figure 1

Analysis of Variance

Comparison of overall composite scores on the NEI VFQ between NC, MCI, and AD clinical classifications did not reveal statistically significant differences among the three groups (NC mean score = 89.8, MCI mean score = 87.69, and AD mean score = 86.42, P = 0.1869). Individual NEI VFQ subscale scores were compared between participant clinical classifications (NC, MCI, and AD) using a Kruskal-Wallis test. This demonstrated a statistically significant difference among the three diagnosis groups in the vision-specific role limitations subscale (NC mean score = 95, MCI mean score = 90.35, and AD mean score = 82.03, P = 0.04). There were no statistically significant relationships observed between the remaining NEI VFQ subscale scores and participant clinical classifications. Lastly, the comparison of overall composite scores on the NEI VFQ and ophthalmic disease classifications was not statistically significant (P = 0.8157).

Discussion

The purpose of this study was to test the utility of the NEI VFQ as a supplemental tool in addressing vision-related problems associated with AD in the primary care setting. The results indicate a statistically significant correlation between cognitive function (based on MMSE score) and self-reported visual function (based on NEI VFQ score). Specifically, as cognitive function increases, self-reported visual function also increases. Furthermore, the study demonstrated a statistically significant difference between participants with NC, MCI, and AD in regard to the vision-specific role limitations subscale. This finding reveals that with worsening cognitive dysfunction, participants report increased limitations and lack of accomplishment because of their eyesight. Because cognitive dysfunction and visual impairment often coexist in the elderly population, and are shown to be correlated, reduced visual function should raise concern for cognitive decline and prompt additional assessment.

There are several limitations to address in this study. This is an epidemiological study – the number of participants in the MCI and AD classifications was relatively small and the sample was predominately female. The study would be stronger with a larger sample size and a more equal sex distribution. Moreover, a larger sample size would allow the study to attain a higher statistical power (while still maintaining a 5% type I error rate). Finally, this project is a cross-sectional study – it does not capture longitudinal data and thus cannot assess trends over time.

Despite these limitations, this research study took advantage of a unique opportunity to collect robust data by leveraging the ADPC infrastructure. This was the first-ever study to report NEI VFQ and MMSE for AD screening. The current findings highlight the need to more fully characterize the relationship between cognitive dysfunction and visual function in the elderly population.

Future Directions

Currently, we plan on implementing the NEI VFQ into the Health and Aging Brain among Latino Elders (HABLE) study, which is a more comprehensive and community-based research study that is enrolling Mexican Americans and non-Hispanic Whites.

Future longitudinal studies will capture longitudinal data to assess changes in trends over time. In addition, future studies will study the relationship between domain-specific neuropsychological testing and visual function and delineate the impact of biomarkers on visual function.

A future application of the study results could assess the impact of intervention on the relationship between cognition and visual function. That is, does treatment and subsequent improvement of age-related ocular conditions lead to improvement in cognition?

The long-term goal is to validate and include ocular biomarkers as components of the multi-faceted neurodiagnostic algorithm for AD. Furthermore, the identification of visual dysfunction in patients, regardless of their level of cognitive dysfunction, provides an opportunity to address those deficits via optical correction, low-vision devices, or disease therapy. These interventions have the potential to reduce the risk of visual disability and improve the HRQOL in patients with AD, thus decreasing individual and societal burden of the disease.

Conclusions

Implementation of effective screening tools such as the NEI VFQ for elderly patients or patients with cognitive dysfunction can help identify reduced visual function. If the etiology is a treatable ocular condition, then interventions such as refractive correction, cataract surgery, or low vision devices could both improve HRQOL and have the potential to improve cognitive outcomes as well. For example, a study evaluating the effect of cataract surgery on cognitive function and depressive mental status of elderly patients identified that vision-related quality of life, cognitive impairment, and depressive mental status were all strongly interrelated, and that cataract surgery led to a significant improvement in vision-related quality of life. This in turn also improved cognitive impairment and depressive mental status in those individuals. [22]

The ability to identify visual impairment in patients over multiple dimensions of health-related quality of life will give health care providers the opportunity to improve that HRQOL via interventions. The visual deficits can be addressed vis optical correction, low-vision devices, or disease therapy.

The NEI VFQ-25 could be implemented as a screening tool in the clinics of primary care physicians to improve the generally poor detection of AD in primary care settings.[16] This would be an opportunity to integrate care among eye care providers and primary care physicians by identifying geriatric patients at risk for cognitive dysfunction and treating them in a timely and appropriate manner.

Compliance

The research protocol for this project was approved by the North Texas Regional Institutional Review Board (IRB). Each participant provided written informed consent in order to engage in the study. This research followed the tenets of the Declaration of Helsinki. As a student researcher, I completed CITI training and worked with de-identified data.

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