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Association between Primary Open-Angle Glaucoma and Cognitive Impairment as Measured by the Montreal Cognitive Assessment

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Cognitive impairment · Glaucoma · Vision · Montreal Cognitive Assessment · Dementia · African American

Abstract
Background: It is currently unclear whether primary open-angle glaucoma (POAG) affects neurological functions outside of vision, such as cognition. ***Objective:*** This study examined the association between POAG and cognitive impairment in African Americans. ***Methods:*** Masked interviewers administered the Montreal Cognitive Assessment (MoCA) to patients enrolled in the Primary Open-Angle African American Glaucoma Genetics (POAAGG) study at the Scheie Eye Institute. Cases were further assessed for retinal nerve fiber layer (RNFL) thickness and visual field (VF) loss. Univariate and multivariate linear regression analyses were performed to compare mean MoCA score between cases and controls and to assess the association between POAG severity and MoCA score. ***Results:*** A total of 137 patients completed the MoCA, including 70 cases and 67 controls. The mean age ± SD was 68.7 ± 11.2 years for cases and 65.7 ± 10.4 years for controls ($p = 0.11$). The mean MoCA total score (out of 30 points) was 20.3 among POAG cases and 21.3 among controls (mean difference = –1.03, 95% confidence interval, CI = –2.54 to 0.48, $p = 0.18$). After adjusting for age, gender, education level, diabetes, hypertension, and smoking status, the mean difference in the MoCA total score between cases and controls was –0.64 (95% CI = –1.72 to 0.45, $p = 0.25$). Among cases, more VF loss was associated with lower total MoCA score for mean deviation (adjusted linear trend $p = 0.02$) and VF index (adjusted linear trend $p = 0.03$). There was no significant association between average RNFL thickness and total MoCA score. ***Conclusions:*** POAG cases and controls had similar neurocognitive function as measured by the MoCA. Among POAG cases, worse VF loss was associated with lower MoCA. Future studies are needed to further elucidate the clinical effect of neuropathy in POAG.

Introduction

Primary open-angle glaucoma (POAG) is the leading cause of irreversible vision loss worldwide, with nearly 60 million people predicted to be affected by 2020 [1]. POAG can be characterized as an optic neuropathy, which develops as retinal ganglion cell damage and optic nerve de-

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generation with subsequent progressive, irreversible vision loss [2]. Several factors increase an individual's risk of developing POAG, including advanced age, increased intraocular pressure (IOP), positive family history, and African American race [3, 4]. However, the exact mechanisms of POAG development are yet to be fully elucidated. It has been suggested that POAG and cognitive impairment may be associated, since both are age-related neurodegenerative processes [5–7]. Multiple mechanisms of associated pathophysiology or common risk factors between dementia and glaucoma have been proposed, including intracranial pressure changes associated with elevated IOP, optic nerve subarachnoid space changes, and β-amyloid deposits [8].

Neurodegeneration in POAG is characterized by loss of retinal ganglion cells [2]. While lowering of IOP, either medically or surgically, has been shown to be effective at preventing progression of vision loss [9], many glaucoma patients suffer continued visual deterioration in spite of IOP control [10, 11]. This suggests that factors besides IOP may play a role in the pathogenesis of vision loss in glaucoma and has sparked interest in other mechanisms for the treatment of POAG, including the use of neuroprotective agents [12, 13]. Recent literature has shown that POAG is associated with neuropathy throughout the visual pathway from the optic nerve through the lateral geniculate nucleus to the visual cortex [14, 15]. However, it remains unclear whether neurodegeneration in glaucoma affects other neurological functions, such as cognition, in addition to vision.

Recent data published by Zheng et al. [16] demonstrated that general visual impairment is associated with worsened cognitive function. Additionally, studies conducted on age-related macular degeneration have demonstrated a possible association between disease progression and lower scores on cognitive function testing [7, 17, 18]. Similarly, studies in open-angle glaucoma have shown an association between POAG and dementia diagnoses, specifically Alzheimer dementia [19, 20]. Other studies have examined RNFL thickness, a measurement of optic nerve degeneration in glaucoma and other optic neuropathies, demonstrating an association between RNFL thinning and dementia [21, 22]. Recent work by Khawaja et al. [23] showed that RNFL thickness was associated with cognitive function, with thicker RNFL measurements correlating with higher scores on cognitive function testing, including the short-form Mini Mental State Examination (MMSE).

This study examined the potential association between POAG and cognitive impairment, with the goal of determining whether certain domains of cognitive function are specifically impacted in POAG. We examined this association among POAG patients and healthy controls recruited in the Primary Open-Angle African American Glaucoma Genetics (POAAGG) study, a 5-year, National Eye Institute-funded study investigating the genetics of POAG in African Americans [24]. Within this cohort, we compared cognitive function between POAG patients and healthy controls and also examined the association between POAG severity and level of cognitive impairment using the Montreal Cognitive Assessment (MoCA).

Methods

Study Population

Participants in this study were recruited from the larger POAAGG study. In brief, eligibility criteria for the POAAGG study included self-identification as black (African American, African descent, or African Caribbean) and age 35 years or older. Eligible participants were recruited during regularly scheduled visits to ophthalmologists at the University of Pennsylvania Scheie Eye Institute and satellites, as well as several neighboring ophthalmology clinics (Temple University, Windell Murphy, MD, USA). Fellowship-trained glaucoma specialists classified subjects as cases, controls, or suspects based on detailed clinical criteria [24]. In brief, cases were defined as having an open iridocorneal angle and characteristic optic nerve defects with corresponding visual field (VF) loss, while controls exhibited a lack of confounding ocular conditions. The POAAGG study design, baseline demographics, complete eligibility criteria, and phenotyping methods have been extensively described [24]. The study protocol and consent statement were approved by the University of Pennsylvania institutional review board.

For this study, patients already enrolled as cases or controls in the POAAGG study were re-approached to undergo MoCA cognitive function testing during regularly scheduled visits to ophthalmologists at the Scheie Eye Institute between June 2016 and August 2017. A total of 165 subjects were approached, of which 137 (70 POAG cases and 67 controls) chose to participate and 28 (20 POAG cases and 8 controls) declined to participate.

Cognitive Assessment

Cognitive function was assessed using the MoCA, a screening test developed to detect mild cognitive impairment (MCI). The MoCA has previously been shown to be a valid, sensitive, and specific tool for the detection of MCI, with better sensitivity for MCI than the MMSE [25]. The MoCA takes less than 15 min to administer and assesses patients in 7 domains of cognitive function: visuospatial/executive function, naming, memory, attention, language, abstraction, and orientation. Patients received a total score out of possible 30 points, as well as a subscore for each domain, with a lower score indicating worse cognitive function. Population-based, age- and education-stratified, normative data for the MoCA published by Rossetti et al. [26] were used for score comparison.

Two investigators administered the MoCA to all participants. Both investigators were blinded to patient diagnostic status (case

Table 1. Baseline demographics and clinical characteristics of POAG cases and healthy controls

	POAG cases (n = 70)	Healthy controls (n = 67)	p value
Age, years			0.11
Mean (SD)	68.7 (11.2)	65.7 (10.4)	
Gender			0.047
Female	40 (57.1%)	50 (74.6%)	
Male	30 (42.9%)	17 (25.4%)	
Education			0.68
Completed graduate degree	6 (8.6%)	3 (4.5%)	
Completed 4-year degree	11 (15.7%)	9 (13.4%)	
Some college	25 (35.7%)	23 (34.3%)	
Completed high school	16 (22.9%)	22 (32.8%)	
Less than high school	12 (17.1%)	10 (14.9%)	
Known dementia diagnosis			0.21
No	65 (92.9%)	66 (98.5%)	
Yes	5 (7.1%)	1 (1.5%)	
Diabetes			0.61
No	42 (60.0%)	37 (55.2%)	
Yes	28 (40.0%)	30 (44.8%)	
Hypertension			0.69
No	18 (25.7%)	15 (22.4%)	
Yes	52 (74.3%)	52 (77.6%)	
History of tobacco use			0.73
No	27 (39.1%)	28 (42.4%)	
Yes	42 (60.9%)	38 (57.6%)	
Smoking status			0.84
Current	9 (13.0%)	9 (14.1%)	
Former	33 (47.8%)	27 (42.2%)	
Never	27 (39.1%)	28 (43.8%)	

One patient in each group had missing data in the history of tobacco use. One POAG case and 3 healthy controls had missing data in smoking status. The t test was used to compare means and the Fisher exact test for proportions.

or control) and other ophthalmic testing data. Additional patient demographics and clinical characteristics, including sex, age, medical history, social history, as well as ophthalmic testing data, including RNFL thickness measurements using optical coherence tomography (OCT) and VF testing results, were obtained from medical records and from participant responses to an initial POAAGG enrollment questionnaire. Because patients for this investigation were recruited from the POAAGG study, only existing, prior test results were used, and no additional VF or OCT testing was done at the time of cognitive assessment.

Ophthalmic Assessment

Disease severity was evaluated for POAG cases using VF and OCT testing. VF were assessed using mean deviation (MD), pattern standard deviation (PSD), and VF index (VFI). VF severity was also determined by a fellowship-trained glaucoma specialist using the 2011 American Glaucoma Society ICD glaucoma severity codes [27]. RNFL thickness was measured using OCT.

Statistical Analysis

We compared the demographic and clinical characteristics between POAG cases and controls using a 2-sample t test for means and Fisher exact test for proportions. We used generalized linear models for comparing MoCA total and subscale scores between POAG cases and controls without and with adjustment by covariates (age, gender, education level, diabetes, hypertension, and smoking status). Among the POAG cases, we evaluated the association of glaucoma severity measures (MD, PSD, VFI, and RNFL thickness) with MoCA score using generalized linear models without and with adjustment by covariates (age, gender, education level, diabetes, hypertension, and smoking status). As glaucoma severity measures were eye specific, the inter-eye correlation was accounted for by using the generalized estimating equations. In these analyses, glaucoma severity measures were categorized into 4 levels using quartiles, and p values for tests of linear trend were calculated. All statistical analyses were performed in SAS V9.4 (SAS Institute Inc., Cary, NC, USA), and two-sided $p < 0.05$ is considered statistically significant.

Table 2. Univariate and multivariate analyses for POAG status and other factors with total MoCA score

Factors	*n*	Mean (SD)	Univariate analysis			Multivariate analysis		
			difference (95% CI)	*p* value	overall *p* value	difference (95% CI)	*p* value	overall *p* value
Group								
Cases	70	20.3 (4.7)	−1.0 (−2.5, 0.5)	0.18		−0.6 (−1.7, 0.5)	0.25	
Controls	67	21.3 (4.4)	reference			reference		
Age (per year)			−0.2 (−0.3, −0.1)	<0.001		−0.1 (−0.2, −0.1)	<0.001	
Gender								
Females	90	21.6 (4.3)	2.3 (0.7, 3.8)	0.004		1.6 (0.4, 2.8)	0.009	
Males	47	19.3 (4.7)	reference			reference		
Education								
Completed graduate degree	9	24.6 (1.6)	9.2 (6.4, 11.9)	<0.001	<0.001	9.2 (6.8, 11.7)	<0.001	<0.001
Completed 4-year degree	20	23.9 (3.8)	8.5 (6.4, 10.6)	<0.001		7.3 (5.3, 9.34)	<0.001	
Some college	48	22.4 (3.0)	7.0 (5.2, 8.8)	<0.001		5.5 (3.8, 7.2)	<0.001	
Completed high school	38	19.5 (3.3)	4.0 (2.2, 5.9)	<0.001		3.5 (1.9, 5.2)	<0.001	
Less than high school	22	15.4 (5.1)	reference			reference		
Diabetes								
Yes	58	19.8 (5.0)	−1.8 (−3.3, −0.3)	0.022		−0.4 (−1.6, 0.7)	0.44	
No	79	21.6 (4.0)	reference			reference		
Hypertension								
Yes	104	20.6 (4.8)	−0.8 (−2.6, 1.0)	0.388		0.3 (−1.1, 1.8)	0.64	
No	33	21.4 (3.6)	reference			reference		
Smoking status								
Former	60	20.2 (4.9)	−0.9 (−2.6, 0.7)	0.28	0.46	0.1 (−1.1, 1.3)	0.84	0.45
Current	18	21.3 (5.1)	0.1 (−2.3, 2.6)	0.90		1.1 (−0.6, 2.8)	0.21	
Never	55	21.2 (4.1)	reference			reference		

Multivariate analysis included all the variables listed in this table.

Results

The MoCA test was administered to a total of 137 participants, including 70 POAG cases (51%) and 67 healthy controls (49%). The mean age ± standard deviation (SD) was 68.7 ± 11.2 years for cases and 65.7 ± 10.4 years for controls (p = 0.11). A higher percentage of cases were male compared to controls (43 vs. 25%, p = 0.047). POAG cases and controls were similar in other demographic and clinical characteristics, including educational background and history of dementia, diabetes, hypertension, and tobacco use (Table 1). A total of 6 patients, including 5 cases and 1 control, had a known diagnosis of dementia.

In univariate analysis, the mean MoCA total score was 20.3 in POAG cases and 21.3 in controls (mean difference = –1.03, 95% CI = –2.54 to 0.48, p = 0.18). In multivariate analysis (adjusting for age, gender, education level, diabetes, hypertension, and smoking status), the mean difference in the MoCA total score between POAG cases and controls was –0.64 (95% CI = –1.72 to 0.45, p = 0.25). Older age and lower education level were significantly associated with lower MoCA score ($p \leq 0.01$) in multivariate analysis (Table 2).

When MoCA subscale scores were examined, no statistically significant difference between cases and controls was found in univariate analysis (Table 3). However, in multivariate analysis, POAG cases had significantly lower attention subscale scores (mean difference = –0.45, 95% CI = –0.83 to –0.06, p = 0.02, Table 3).

Among POAG cases (n = 70), prior VF data were available for 65 patients (128 eyes). Of these, Humphrey perimetry testing (HVF) was used for 48 patients (94 eyes), Octopus (OVF) was used for 13 patients (26 eyes), and Goldmann was used for 5 patients (9 eyes). From the HVF reports, MD and PSD were available for 92 eyes, and VFI was available for 79 eyes. The reliability of the HVF tests was assessed based on the frequency of false-positive and false-negative results and the percentage of fixation errors. HVF tests with fixation losses, false positives, or false negatives greater than 20% were considered unreliable and were excluded from the analysis. Reports for 81 eyes were considered reliable, and 13 eyes were

Table 3. Univariate and multivariate analyses for the comparison of MoCA subscales between POAG cases and controls

MoCA subscale	Group	*n*	Mean (SD)	Univariate analysis		Multivariate analysis[1]	
				difference (95% CI)	*p* value	difference (95% CI)	*p* value
Abstraction	Cases	70	0.86 (0.82)	0.02 (–0.24, 0.29)	0.88	–0.00 (–0.26, 0.26)	1.00
	Controls	67	0.84 (0.77)	reference		reference	
Attention	Cases	70	4.47 (1.37)	–0.39 (–0.84, 0.05)	0.09	–0.45 (–0.83, –0.06)	*0.02*
	Controls	67	4.87 (1.32)	reference		reference	
Delayed recall	Cases	70	2.20 (1.70)	–0.19 (–0.73, 0.36)	0.50	0.11 (–0.40, 0.62)	0.68
	Controls	67	2.39 (1.57)	reference		reference	
Language	Cases	70	1.74 (0.85)	–0.11 (–0.42, 0.21)	0.50	–0.10 (–0.37, 0.17)	0.48
	Controls	67	1.85 (1.03)	reference		reference	
Naming	Cases	69	2.58 (0.72)	–0.00 (–0.24, 0.23)	0.98	0.02 (–0.20, 0.24)	0.87
	Controls	67	2.58 (0.70)	reference		reference	
Orientation	Cases	70	5.63 (0.90)	–0.21 (–0.45, 0.03)	0.09	–0.14 (–0.37, 0.09)	0.23
	Controls	67	5.84 (0.45)	reference		reference	
Visuospatial/executive	Cases	69	2.86 (1.31)	–0.13 (–0.56, 0.30)	0.56	–0.09 (–0.46, 0.29)	0.64
	Controls	67	2.99 (1.29)	reference		reference	

[1] Adjusted model includes age, gender, education, diabetes, hypertension, and smoking status as covariates.

Table 4. Univariate and multivariate analyses for associations of glaucoma severity with total MoCA score in patients with HVF data

POAG severity	Level	Eyes, *n*	Mean (SD)	Unadjusted analysis			Adjusted analysis		
				difference (95% CI)	*p* value		difference (95% CI)	*p* value	
MD	≥–1.2	24	21.9 (4.0)	4.0 (1.1, 6.9)	0.007	0.008[1]	2.1 (0.3, 3.9)	0.02	0.02[1]
	–4.6 to –1.2	22	20.9 (3.5)	3.0 (0.4, 5.6)	0.03		0.8 (–1.1, 2.7)	0.41	
	–13.2 to –4.6	23	18.3 (5.0)	0.4 (–2.8, 3.6)	0.81		–0.9 (–2.4, 0.6)	0.24	
	–34.4 to –13.2	23	17.9 (4.3)	reference			reference		
PSD	≥7.8	23	19.1 (4.4)	–2.5 (–4.9, –0.1)	0.04	0.03[1]	–0.8 (–2.5, 0.9)	0.38	0.17[1]
	3.8–7.8	23	18.1 (5.0)	–3.5 (–6.3, –0.7)	0.02		–1.7 (–3.4, 0.0)	0.05	
	2.0–3.8	22	20.1 (4.7)	–1.5 (–3.7, 0.8)	0.19		0.1 (–1.3, 1.6)	0.86	
	1.0–2.0	24	21.6 (3.3)	reference			reference		
VFI	≥98%	22	21.8 (4.2)	4.4 (1.4, 7.4)	0.004	0.01[1]	2.2 (0.4, 4.0)	0.02	0.03[1]
	92–98%	18	21.2 (3.8)	3.8 (1.0, 6.5)	0.008		1.4 (–0.7, 3.4)	0.18	
	70–92%	20	19.9 (4.4)	2.5 (–0.2, 5.3)	0.07		0.3 (–1.1, 1.7)	0.67	
	2–70%	19	17.4 (4.3)	reference			reference		
Severity	Severe	56	19.2 (4.6)	–1.8 (–4.0, 0.4)	0.12	0.09[1]	–0.6 (–2.2, 1/0)	0.47	0.50[1]
	Moderate	21	20.7 (4.8)	–0.3 (–3.0, 2.4)	0.85		–0.4 (–2.4, 1.5)	0.67	
	Mild	16	20.9 (3.7)	reference			reference		
RNFL	≥82.0	34	19.6 (4.4)	0.0 (–2.6, 2.7)	0.97	0.873[1]	–1.3 (–3.3, 0.7)	0.21	0.18[1]
	70.0–82.0	33	21.3 (4.6)	1.8 (–0.89, 4.40)	0.19		0.2 (–1.7, 2.1)	0.84	
	62.5–70.0	32	20.7 (4.9)	1.1 (–1.6, 3.9)	0.41		0.8 (–1.1, 2.6)	0.41	
	51.0–62.5	33	19.6 (5.1)	reference			reference		

The adjusted model includes age, gender, education, diabetes, hypertension, and smoking status as covariates. [1] Linear trend.

determined to have unreliable VF reports. In both univariate and multivariate analyses of HVF results, more VF loss was significantly associated with lower total MoCA score for MD (adjusted linear trend $p = 0.02$) and VFI (adjusted linear trend $p = 0.03$) (Table 4). The adjusted mean difference in MoCA scores between the 1st (higher MD) and 4th quartiles (lower MD) for MD was 2.0 points (95% CI = 0.3–3.9, $p = 0.02$), and the adjusted mean difference in MoCA scores between the 1st (higher VFI) and 4th quartiles (lower VFI) was 2.2 points (95% CI = 0.4–4.0, $p = 0.02$). Lower PSD was significantly associated with higher total MoCA score in univariate analysis (linear trend $p = 0.03$) but nonsignificant in multivariate analysis (adjusted linear trend $p = 0.17$). When POAG severity was categorized using the ICD glaucoma severity codes, 56 cases were classified as severe, 21 as moderate, and 16 as mild. In both univariate and multivariate analysis, there was no statistically significant association between POAG severity classification and total MoCA score.

Average RNFL thickness data from OCT were available from 66 POAG cases (132 eyes). In univariate and multivariate analysis, there was no significant association between RNFL thickness and total MoCA score (Table 4).

Discussion

This study examined the association of cognitive function (measured by the sensitive and valid MoCA) with POAG status and its severity in an African American population. We found no significant difference in total MoCA score between POAG cases and healthy controls, nor any significant association between RNFL thickness and total MoCA score. However, a subtle association between VF and cognitive function was detected among POAG patients.

Though total MoCA score did not differ between cases and controls, these groups did experience a significant difference in the attention subsection score. This section asked patients to repeat strings of digits in forward and backward order; to identify and signal each time they hear a specified letter in a string of letters read aloud; and to perform serial subtractions (for a subscore out of 5 points). This result may suggest that certain cognitive abilities, such as the short-term memory, computational skills, and cognitive focus and attention tested in this subsection, may be impaired in glaucoma. Notably, none of the activities in the attention subsection required the use of vision, which reduces the likelihood that this difference could be attributed to impaired vision in POAG cases compared to controls.

This study also demonstrated a subtle association between VF deficits and cognitive function among POAG patients. This result may indicate that more severe glaucoma, as indicated by more severe VF loss, is associated with worse cognitive function as measured by the MoCA. However, this finding may also be explained by poor vision and narrowed VF affecting a patient's performance on the MoCA, especially on sections that require the use of vision for reading and writing. Additionally, it is also possible that poor cognition can affect the reliability and variability of VF testing results [28]. This further complicates the association between VF loss in glaucoma and cognitive function. Thus, the role of VF loss in glaucoma as a possible marker of global neurodegeneration warrants further investigation to evaluate any clinical significance.

Given the results of this study, the association between glaucoma and global cognition remains unclear. Neurodegeneration associated with glaucoma may be limited to the visual pathway and may not extend more globally in the brain to affect neural pathways involved in cognition. It is also possible that patients who declined to participate in this study ($n = 28$; 17% of total patients approached) when approached for MoCA testing may have chosen to decline for reasons that could bias the results of this study, such as insecurities regarding perceived or diagnosed memory loss or cognitive difficulties. Most patients declined MoCA testing because of lack of time or interest. However, 1 patient declined to participate due to a recent diagnosis of dementia. It is possible that POAG patients with dementia may be less likely to seek vision care than those without cognitive impairment, and therefore such patients may be less accessible for inclusion in this type of study. Finally, it is possible that only a subset of patients manifest cognitive impairment associated with POAG; a larger study cohort would be necessary to elucidate such a relationship.

It should be noted that this study consisted of an entirely African American patient cohort. Since POAG is more common among African Americans, this is an important population in the ongoing study of open-angle glaucoma. However, the results of this study may not be generalizable to other populations or reflect an association between cognitive function and POAG that is applicable to all patients.

In summary, this study did not demonstrate a clear relationship between POAG and overall neurocognitive function. However, the results did show a subtle associa-

tion between cognitive attention function and POAG, as well as a small association between worse VF loss and lower MoCA scores. Future studies are needed to further understand the effect of central nervous system neuropathy on neurocognition in POAG.

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Disclosure Statement

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