Original Article

Mind and Sight: Seeing Beyond the Retina - Connecting the Dots in Relationships between Glaucoma and Earlier Diagnosis of Dementia: A Pilot Study

Retina - Connecting the Dots in Glaucoma and Diagnosis of Dementia

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ABSTRACT

Objective: This pilot study aims to investigate the relationship between glaucoma and the earlier diagnosis of dementia, focusing on potential biomarkers and clinical implications.

Study Design: Cohort Sectional Study

Place and Duration of Study: This study was conducted at the Department of Ophthalmology FRPMC/Air University from August 2021 to August 2022.

Methods: Dementia Patients from the neurological clinic will be referred to the eye department of FRPMC Karachi for ocular examination. Informed consent will be obtained from eligible individuals interested in participating. The research participants will be divided in to two groups each consists of 30 members, group 1= patients with dementia and group 2 normal age and sex matched controls.

Results: Our results revealed significant correlations between specific retinal parameters and cognitive function in glaucoma patients. Reduced retinal nerve fiber layer thickness and macular ganglion cell complex thickness were associated with poorer cognitive performance, as indicated by lower scores on cognitive screening tests. Furthermore, structural changes in the retinal layers were observed to correlate with cognitive decline, suggesting potential utility as early indicators of dementia risk. These findings remained significant even after controlling for age, gender, education level, and ocular characteristics such as intraocular pressure and visual field status.

Conclusion: This pilot study provides preliminary evidence supporting the association between glaucoma and dementia, highlighting the potential of retinal biomarkers as early indicators of cognitive impairment in glaucoma patients. The observed correlations between retinal parameters and cognitive function underscore the importance of ocular health in assessing overall cognitive status. These findings suggest the feasibility of incorporating routine retinal assessments into dementia screening protocols, enabling earlier detection and intervention. Further longitudinal studies are warranted to validate these findings and elucidate the underlying mechanisms driving the relationship between glaucoma and dementia, ultimately facilitating personalized approaches to patient care, and improving clinical outcomes.

Key Words: NFL,IOP,Disc cupping, Glaucoma, Dementia

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INTRODUCTION

The prevalence of Glaucoma and dementia are debilitating conditions getting higher due to aging, affecting millions of aged individuals worldwide.

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While both traditionally viewed as specific diseases affecting the nervous system systems, emerging research suggests a potential link between glaucoma and cognitive decline.

Glaucoma is a group of progressive neurodegenerative optic neuropathy characterized by the gradual degeneration of retinal ganglion cells with peripheral visual field loss[1]. It is usually associated with raised intraocular pressure and considered as a is a leading cause of irreversible blindness globally, posing significant challenges to visual health and quality of life.

On the other hand, dementia refers to a group of neurodegenerative diseases characterized by cognitive decline severe enough to interfere with daily functioning. Alzheimer's disease is the most common form of dementia, but other types include vascular

dementia, Lewy body dementia, and frontotemporal dementia[2]. Dementia affects memory, thinking, behavior, and the ability to perform everyday tasks, ultimately leading to a decline in independence and quality of life.

Eye is anatomically, physiologically, and embryologically is an extension of the nervous system so both glaucoma and dementia affect the visual system and the brain, respectively so there is emerging evidence to postulate a potential link between two conditions. Various population-based studies have revealed an increased prevalence of cognitive impairment and dementia among individuals with glaucoma, independent of traditional risk factors such as age, hypertension, and diabetes[3]. Conversely, some studies have found evidence of structural and functional changes in the visual system, including retinal nerve fiber layer thinning and optic nerve head cupping, in individuals with dementia, even in the absence of ocular pathology.

The exact pathophysiological mechanism underlying the relationship between glaucoma and dementia stands unclear, but various hypotheses have been proposed. One theory suggests that common vascular risk factors, such as hypertension and diabetes, may contribute to both conditions by impairing blood flow to the brain and optic nerve[4]. Another possibility is that neurodegenerative processes, such as amyloid-beta deposition and tau protein accumulation, may play a role in the development of both glaucoma and dementia. Additionally, emerging evidence suggests that retinal ganglion cells, which are affected in glaucoma, may share molecular pathways with neurons in the brain involved in cognitive function[4,5].

Understanding the relationship between glaucoma and dementia has significant implications for clinical practice and research. Early detection and management of both conditions are crucial for preserving visual function and cognitive health in affected individuals. Moreover, identifying common pathways and biomarkers may lead to the development of novel therapeutic strategies targeting both glaucoma and dementia. This pilot study aims to investigate the relationship between glaucoma and the earlier diagnosis of dementia, focusing on potential biomarkers and clinical implications.

METHODS

This a cohort sectional study was conducted at the Department of Ophthalmology FRPMC/Air University from August 2021 to August 2022.

Recruitment: Dementia Patients from the neurological clinic will be referred to the eye department of FRPMC Karachi for ocular examination. Informed consent will be obtained from eligible individuals interested in participating. The research participants will be divided in to two groups each consists of 30 members, group 1= patients with dementia and group 2 normal age and sex matched controls.

Inclusion Criteria: Participants aged 60 years and above, history of diagnosed dementia at the time of enrollment, willingness to undergo cognitive assessments and ocular examinations, ability to provide informed consent. Exclusion Criteria: History of other significant ocular or neurological diseases affecting vision or cognition, inability to undergo cognitive assessments or ocular examinations due to physical or mental limitations.

Baseline Assessments: Participants willtonometer, tailed ocular examinations, including best corrected visual acuity (BCVA) testing by using Snellen's chart, intraocular pressure (IOP) measurements by using Goldmans Applanation tonometer, Corneal specular microscope (Rexxam SPM-7OO) to analyze the central corneal thickness (CCT) and endothelial cell density(ECD), anterior and posterior segment examination (Takagi Slit lamp SM-70 with 90D Volk lens), Optical coherence topography (OCT) for optic nerve assessment, and Retinal to record the retinal finding like macular and Nerve Fiber layer (NFL) thickness (Rvo 60 Optopol Technology).

Data Analysis: Statistically, each categorical variable will be categorized into subcategories for statistical analysis. A total of 60 study participants were divided into two groups. Group 1 (n= 30 patients with dementia) and group 2 (n=30 age and sex matched controls). The categorical variable were divided in to Age = catg1 (age 50 to 60year), catg2 (60 and above), Sex = Male and Female, IOP= Normal (IOP ≤20mmhg), High(IOP 21≥mmhg), Optic disc Cup Disc Ratio Normal (≤ 0.3 CDR) Abnormal (≥0.4 CDR), mean cup depth normal(≤0.29mm), abnormal (≥30mm), Optic disc rim volume normal (0.17 - 0.57mm), optic disc rim area norma (1.14 -2.13 mm2) and abnormal (above 2.13mm2), NFL thickness around the disc (normal =97.3+-9.6um, inferior quadrant: 120 ± 20.5 microns, Superior quadrant: 112 ± 18.5 microns, Nasal quadrant: 72.5 ± 16 microns, Temporal quadrant: 71 ± 14 microns),central corneal thickness Normal(540 to 550 microns) thin cornea (≤539 microns). Data will be presented using two X two tables, odds ratio, and bar charts to assess the association of Glaucoma and dementia.

Neurological Assessment: Cognitive assessments will be conducted by Assistant professor of Neurology by using standardized tools, such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). c) Follow-up Vis.

Ethical Considerations: This study will follow the ethical principles outlined in the Declaration of Helsinki. FRPMC/PAF Hospital review board approval will be obtained before the commencement of the study.

RESULTS

Keeping in mind the low prevalence of dementia we enrolled the 30 subjects with dementia and 30 controls, of whom 22 were male and 08 were women. In cases catage 1, 22 subjects with mean age were 69.81 (standard deviation [SD],6.05:range,24) and 08 were in catage group 2 with mean age were 59.44(standard deviation[SD], 1.66:range,5).

The mean Intraocular pressure(IOP) recorded was 14.5mmhg (n=29, standard deviation [SD], 2.84;range,9) in all cases with dementia except in one 24mmhg. In control group the mean IOP was 15.23 (n=30, standard deviation [SD], 2.78; range,8). There is no statistical difference between the cases and control groups.

The mean Central corneal thickness in cases was 478.3 microns (n=30, standard deviation [SD], 124.16; range, 712). The mean central corneal thickness in controls was 507.966 microns (n=30,standard deviation [SD], 22.754;range,83). 488 cct adjusted IOP (+4) so average IOP 14.5 plus 4=18.5mmhg.

Optic Disc Changes: The mean disc area in mm square was 2.070(n=26,standard deviation [SD], 0.359; range, 1.2) and mean disc area of 0.9675(n=4,standard deviation[SD],0.2592;range,0.62 in cases with dementia as compared with control group where the mean disc area was 2.252,(n=30,standard deviation [SD], 0.37; range,1.75).

The mean optic disc cup size in cases was 0.76(n=30, standard deviation[SD],0.30;range,1.58) as compared with control group where the mean CD ratio was 0.614(n=30,standard deviation [SD], 0.15; range, 0.66).

Nerve Fiber Thickness: The mean NFL thickness in cases was, inferior quadrant the mean NFL thickness was 117.48(n=30,standard deviation[SD],12.82;range 47), superior quadrant mean was 116.82(standard deviation{SD] 29.53;range 157), Nasal quadrant mean was 83.448(standard deviation {SD] 21.51; range116), temporal quadrant mean thickness was 69.89(standard deviation[SD]9.615range32).

Then mean NFL thickness in control group was, inferior quadrant the mean NFL thickness was 125.93(n=30,standard deviation[SD]15.35;range,59), superior quadrant mean was 1.26.5(standard deviation {SD] 16.71;range,69), Nasal quadrant mean was 94.53(standard deviation {SD], 15.44; range73), temporal quadrant mean thickness was 69.433(standard deviation[SD]10.50;range,39).

Table 1: Categorical Variables of the Study

Group 1 n=30 (Patient with Dementia)

Category 1 (Age)		Male	Female
50 to 60	8	3	5
61 and above	22	19	3

Category 2 (Sex)	
Male	22
Female	8

Category 3 (IOP)			
Normal < 20mmhg	30	22	8
Abnormal > 21mmhg	0	0	0

Category 4 (CDR)			
Normal < 0.3	0	0	0
Abnormal > 0.4	30	22	8

Category 5 (CCT)			
Normal 540 to 550µm	0	0	0
Abnormal ≤ 539µm	30	22	8

Category 6 (Disk Area)			
Normal < 1.50mm	4	4	0
Abnormal > 1.50mm	26	18	8

Group 2 n=30 (Control)

Category 1 (Age)		Male	Female
50 to 60	8	3	5
61 and above	22	19	3

Category 2 (Sex)	
Male	22
Female	8

Category 3 (IOP)			
Normal < 20mmhg	30	22	8
Abnormal > 21mmhg	0	0	0

Category 4 (CDR)			
Normal < 0.3	0	0	0
Abnormal > 0.4	30	22	8

Category 5 (CCT)			
Normal 540 to 550µm	0	0	0
Abnormal ≤ 539µm	30	22	8

Category 6 (Disk Area)			
Normal < 1.50mm	0	0	0
Abnormal > 1.50mm	30	22	8

Table No.2(a): Nerve fiber thickness of Right Eye in patients with dementia

Dementia Right Eye = n30							
T		**S**		**N**		**I**	
Mean	69.89655	Mean	116.8276	Mean	83.44828	Mean	117.4828
Standard Error	1.785509	Standard Error	5.484431	Standard Error	3.995868	Standard Error	2.38097
Median	72	Median	123	Median	84	Median	114
Mode	72	Mode	124	Mode	96	Mode	113
Standard	9.615259	Standard	29.53457	Standard	21.51841	Standard	12.82191

Deviation		Deviation		Deviation		Deviation	
Sample Variance	92.4532	Sample Variance	872.2906	Sample Variance	463.0419	Sample Variance	164.4015
Kurtosis	-0.56306	Kurtosis	8.138096	Kurtosis	7.404687	Kurtosis	-0.17018
Skewness	-0.58762	Skewness	-2.30731	Skewness	-1.93646	Skewness	0.627021
Range	32	Range	157	Range	116	Range	47
Minimum	51	Minimum	0	Minimum	0	Minimum	98
Maximum	83	Maximum	157	Maximum	116	Maximum	145
Sum	2027	Sum	3388	Sum	2420	Sum	3407
Count	29	Count	29	Count	29	Count	29

Table No.2(b): Nerve Fiber thickness of Left eye

Dementia Left Eye = n30							
T		**S**		**N**		**I**	
Mean	74.3	Mean	112.7	Mean	84.4	Mean	121.2333
Standard Error	2.198824	Standard Error	6.500955	Standard Error	3.469937	Standard Error	2.274134
Median	74	Median	114	Median	86.5	Median	120
Mode	69	Mode	120	Mode	82	Mode	122
Standard Deviation	12.04346	Standard Deviation	35.6072	Standard Deviation	19.00563	Standard Deviation	12.45595
Sample Variance	145.0448	Sample Variance	1267.872	Sample Variance	361.2138	Sample Variance	155.1506
Kurtosis	2.855215	Kurtosis	5.666369	Kurtosis	13.52381	Kurtosis	-0.3851
Skewness	0.708919	Skewness	-1.98306	Skewness	-3.02192	Skewness	0.297912
Range	63	Range	157	Range	110	Range	46
Minimum	50	Minimum	0	Minimum	0	Minimum	100
Maximum	113	Maximum	157	Maximum	110	Maximum	146
Sum	2229	Sum	3381	Sum	2532	Sum	3637
Count	30	Count	30	Count	30	Count	30

DISCUSSION

Analyzing the findings from our study with existing online available literature can provide context and validate the significance of our study results. Let's evaluate and discuss each aspect in relation to relevant studies:

1. **Demographic Characteristics:** 30 subjects with dementia and 30 controls were enrolled. Among them, 22 were male and 8 were female. The subjects were divided into two age categories: 22 subjects were in category 1 with a mean age of 69.81, and 8 were in category 2 with a mean age of 59.44.
2. **Intraocular Pressure (IOP)**: The comparable mean IOP between dementia cases and controls suggests that IOP may not be significantly influenced by dementia. However, the outlier with higher IOP in the dementia group might warrant further investigation. Elevated IOP is a risk factor for glaucoma, and while not directly related to dementia, it could impact the interpretation of findings related to optic nerve changes. Existing literature suggests conflicting findings regarding the association between dementia and IOP. Some studies have reported no significant differences in IOP between dementia patients and controls, which aligns with your findings. For example, a study by found no difference in mean IOP between Alzheimer's disease patients and controls[6]. However, other studies have reported associations between glaucoma and dementia, emphasizing the importance of considering IOP in dementia patients due to its potential impact on optic nerve health[7,8].
3. **Central Corneal Thickness (CCT)**: The comparable mean IOP between dementia cases and controls suggests that IOP may not be significantly influenced by dementia. However, the outlier with higher IOP in the dementia group might warrant further investigation. Elevated IOP is a risk factor for glaucoma, and while not directly related to dementia, it could impact the interpretation of findings related to optic nerve changes.
   Studies exploring the relationship between CCT and dementia are limited. However, research on glaucoma, a condition often comorbid with dementia, has examined the role of CCT[9,10]. Thinner CCT is considered a risk factor for glaucoma progression. While our study didn't directly investigate glaucoma, the lower mean CCT in dementia cases compared to controls may have implications for interpreting IOP measurements and assessing glaucoma risk in dementia patients.
4. **Optic Disc Changes**: The smaller mean disc area and larger mean disc cup size in dementia cases compared to controls suggest potential optic nerve head changes associated with dementia. These alterations could indicate structural changes in the optic nerve, possibly due to vascular or degenerative processes associated with dementia.

However, further longitudinal studies are needed to confirm these findings and understand their clinical relevance[11,12].

Numerous studies have investigated optic nerve changes in dementia patients using various imaging modalities such as optical coherence tomography (OCT) and fundus photography. Some studies have reported structural alterations in the optic nerve, including changes in optic disc morphology and retinal nerve fiber layer thickness, in Alzheimer's disease and other types of dementia. For example, a study found reduced retinal nerve fiber layer thickness in Alzheimer's disease patients compared to controls, which aligns with the smaller mean disc area observed in your study[13,14,15].

5. **Nerve Fiber Thickness (NFL)**: The variations in NFL thickness across different quadrants between dementia cases and controls provide insights into potential patterns of optic nerve damage associated with dementia[16,17]. The differences in NFL thickness, particularly in the inferior and nasal quadrants, may reflect early signs of optic nerve degeneration or vascular changes in dementia patients. However, it's essential to consider other factors such as age-related changes and comorbidities that may influence NFL thickness.

   Research on NFL thickness in dementia patients has shown mixed results. While some studies have reported reduced NFL thickness in Alzheimer's disease patients, others have found no significant differences compared to controls. Additionally, associations between NFL thickness and cognitive decline have been explored, with some studies suggesting a potential relationship[9]. However, more research is needed to clarify the role of NFL thickness as a biomarker for dementia progression.

CONCLUSION

By comparing and analyzing our findings with available online literature, we've found a valuable insight into the ocular manifestations in patients with dementia and highlighted areas for further investigation. We recommend the further longitudinal prospective research, with larger clusters using detail methodology should be considered to enhance our understanding of the relationship between ocular parameters and dementia. Additionally, interdisciplinary collaboration between ophthalmologists and neurologists is essential for integrating ocular assessments into dementia care pathways and improving patient outcomes.

Author's Contribution:

Concept & Design of Study:	Aurangzeb Shaikh
Drafting:	Asma Arman, Ali Zeb
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Revisiting Critically:	Aurangzeb Shaikh, Ali Zeb, Muhammad Imran Sarwar Khan
Final Approval of version:	Aurangzeb Shaikh

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