ORIGINAL RESEARCH

A Retrospective Cohort Study on the Difficulties of Diagnosing and Managing Glaucoma in Patients with Coexistent Neurodegenerative Disease

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Received on: 11 April 2023; *Accepted on:* 02 September 2023; *Published on:* 11 October 2023

Abstract

Aim: To investigate the limitations of diagnosing glaucoma in patients with coexistent neurodegenerative disease (NDD) by collecting information on demographics, examination findings, optical coherence tomography (OCT), and visual field (VF) tests.

Materials and methods: Retrospective cohort study of patients with primary open-angle glaucoma and coexistent dementia, multiple sclerosis (MS), Parkinson's disease (PD), or cerebrovascular accident (CVA) from 2014 to 2020. We included patients with a minimum of 3 years of follow-up. Demographics, ophthalmic exam, OCT, and VF findings were reported and compared across NDD groups using the Chi-squared and analysis of variance tests.

Results: We included 199 patients with glaucoma and coexistent NDD, including dementia (51.3%), CVA (11.2%), PD (18.1%), and MS (19.6%). Cupping, neuroretinal rim thinning, pallor, and peripapillary atrophy of the optic nerve were most frequently observed. There was a high number of missing values from OCT to VF tests, and zero patients had a complete OCT or VF test. Additionally, 67.8 and 77.4% of patients received <1 OCT and VF/year, respectively. Retinal nerve fiber layer (RNFL) thinning was observed most frequently in the superior (33.2% OD and 30.7% OS) and inferior (25.6% OD and 30.2% OS) quadrants, with the most significant thinning seen in CVA patients compared to other NDDs ($p < 0.05$). Glaucoma hemifield tests (GHTs) were abnormal in 23.1% OD and 22.6% OS, and the average mean deviation was −7.43 [standard deviation (SD) 8.23] OD and −8.79 (SD 7.99) OS.

Conclusion: The OCT and VF tests are frequently unavailable and may be confounded in patients with coexistent glaucoma and NDDs, complicating glaucoma diagnosis and management.

Clinical significance: Diagnosing and managing glaucoma in patients with coexistent NDD is difficult, given the lack of available and reliable OCT and VF testing data. Providers may be forced to rely on intraocular pressure (IOP) and other imperfect measures.

Keywords: Cerebrovascular accident, Cohort study, Dementia, Glaucoma, Multiple sclerosis, Parkinson's disease.

Journal of Current Glaucoma Practice (2023): 10.5005/jp-journals-10078-1415

Introduction

Glaucoma is a progressive optic neuropathy that results in characteristic optic nerve atrophy and vision loss and is often associated with elevated intraocular pressure (IOP).[1,2] In diagnosing and monitoring glaucoma, visual field (VF) tests are used to determine vision loss and glaucoma severity.[3] Additionally, optical coherence tomography (OCT) and optic nerve photographs are used to monitor the nerve structure, retinal nerve fiber layer (RNFL) thinning, and ganglion cell loss.[3] On fundus exam, the presence of optic disc abnormalities such as thinning, cupping, notching of the disk rim, progressive change, or nerve fiber layer defects are key to diagnosing primary open angle glaucoma (POAG).[3]

Neurodegenerative diseases (NDD) may confound these tests as there are OCT, VF, and optic nerve changes associated with certain NDDs. The literature has demonstrated that Alzheimer's disease results in significant ganglion cell loss, RNFL thinning, and loss of optic nerve axonal projections.[4–6] Similarly, Parkinson's disease (PD) and multiple sclerosis (MS) have also been associated with RNFL thinning and reduction in macular thickness.[4,7,8] Additionally, a cerebrovascular accident (CVA) in the occipital cortex may result in a significant visual field (VF) defect. Vascular conditions, such as vascular dementia, can result in necrotic death of retinal ganglion cell axons, and subsequent optic nerve atrophy may occur in a manner similar to glaucomatous optic atrophy. However, superimposed glaucoma may exist or develop in patients with any of these conditions. Therefore, OCT and VF findings, as well as the optic nerve appearances, are confounded in these patients, limiting the ability to monitor or diagnose glaucoma.

Beyond confounding the results of glaucoma diagnostic tests, NDDs may also limit patients' ability to perform these tests. VF tests

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How to cite this article: Ciociola EC, Patel K, Blahnik T, *et al.* A Retrospective Cohort Study on the Difficulties of Diagnosing and Managing Glaucoma in Patients with Coexistent Neurodegenerative Disease. J Curr Glaucoma Pract 2023;17(3):126–133.

Source of support: Nil

Conflict of interest: None

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require active participation by a patient to follow instructions and respond to stimuli, as well as physical requirements for positioning. Patients with progressing Alzheimer's disease may be unable to retain focus throughout the test, and patients with PD may have difficulty with the positioning required for testing.[9] Therefore, these objective tests essential for diagnosing glaucoma are unable to be utilized.

The purpose of this study was to investigate the limitations of diagnosing glaucoma in patients with coexistent NDD by collecting information on demographics, examination findings, OCT, and VF tests. We suspect a high proportion will have incomplete testing, forcing providers to rely on the few remaining clinical parameters such as IOP.

Materials and Methods

This study was approved by the University of North Carolina Institutional Review Board. A waiver of informed consent was granted. The study met the tenets of the Declaration of Helsinki.

Data Source and Study Population

We retrospectively collected data on patients at the Kittner Eye Center from 1st January 2014 to 2020. We included patients with a diagnosis of POAG and one of the following NDDs—Alzheimer's disease, PD, Lewy body dementia, CVA, frontotemporal dementia, vascular dementia, Creutzfeldt–Jakob disease, neurofibromatosis type 1, Wernicke–Korsakoff syndrome, amyotrophic lateral sclerosis (ALS), multiple system atrophy, progressive supranuclear palsy, normal tension hydrocephalus, or MS. We excluded patients with more than one NDD to disambiguate the results. Additionally, we excluded patients with ocular comorbidities that could impact testing results, including diabetic retinopathy, central retinal vein and artery occlusions, ischemic optic neuropathy, and neovascularization. Patients with closed angles on gonioscopy despite their diagnosis of POAG were excluded due to the inconsistency of these findings. Patients with POAG were included regardless of the laterality of diagnosis because glaucoma is typically a bilateral disease. Additionally, we only included patients who were older than 18 years of age with a minimum of 3 years of follow-up and at least three ophthalmology exam visits.

Data Extraction

The electronic medical record was reviewed to collect patient demographics, NDD, family history of glaucoma, ocular surgical history, and history or current presence of another ophthalmic disease. Additionally, we collected data from the ophthalmic exam, including IOP, visual acuity, central corneal thickness, presence of an afferent pupillary defect (APD), cup-to-disc ratio (CDR), lens status, angle status from gonioscopy, and optic nerve characteristics. IOP was defined as the average of readings from the three most recent visits to account for physiologic IOP variations. At our institution, IOP is measured using either Goldmann applanation, iCare tonometer, or Tono-Pen. All other data were extracted from the most recent ophthalmic exam visit. Data from eye-specific variables were collected and recorded from both eyes to provide more information on these patients (e.g., visual acuity OD, visual acuity OS).

We obtained OCT peripapillary RNFL thickness and optic nerve head measurements using Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, California). CDR, vertical CDR, disk area, average thickness, RNFL symmetry, and the percentage of patients with borderline or thin RNFL quadrants were collected from OCT imaging. VFs were obtained using Humphrey field analyzer (Zeiss Meditech) 24-2 Swedish Interactive Threshold Algorithm (SITA) testing (varied between standard and fast). We collected mean deviation, pattern standard deviation, glaucoma hemifield test (GHT), fixation losses, false negatives, and false positives from the VF tests. OCT and VF data were collected from the most recent tests in the system. These tests were defined as incomplete if they had some, but not all, OCT or VF variables available. Patients were defined as unable to complete testing if there was documentation in the electronic medical record of their inability to complete testing related to their NDD, such as the inability to maintain fixation, posture, or attention. The number of tests per year was calculated by dividing the number of tests by the number of years since the initial glaucoma eye exam visit.

Statistical Analysis

Demographics, NDD type, ocular comorbidities, and ophthalmic surgical history were reported for all patients in Table 1. We expressed continuous variables using means and standard deviation (SD) and categorical variables using frequencies and percentages. Ophthalmic exam features, OCT measurements, and VF parameters were compared with analysis of variance tests for continuous variables and Chi-squared tests for categorical variables among NDD groups. The analysis was done at the patient level rather than the eye level to avoid bias introduced by intereye correlations. We considered a p-value < 0.05 as statistically significant. We performed all statistical analyzes using Stata version 15.1 (StataCorp, LP, College Station, TX).

Results

We included 199 patients with a diagnosis of POAG and coexistent NDD, including patients with dementia (n = 102, 51.3%), CVA (n = 22, 11.1%), PD (n = 36, 18.1%), and MS (n = 39, 19.6%) (Table 1). We excluded 11 patients with ALS, Creutzfeldt–Jakob disease, neurofibromatosis type 1, multiple system atrophy, or traumatic brain injury due to the low number of patients with each diagnosis. Additionally, we excluded 22 patients who were noted to have multiple NDDs (e.g., stroke and dementia) to disambiguate the results. We excluded 28 patients with ocular comorbidities (ischemic optic neuropathy, retinal vein and artery occlusions, diabetic retinopathy, and neovascularization) that could impact testing results. Finally, we excluded three patients with closed angles on gonioscopy. Patients with vascular dementia, Alzheimer's disease, or unspecified dementia were grouped into one overarching dementia category because of the limited number of patients in the dementia subcategories. Half of the cohort was female (55.3%), and the average age was 76 years old. Approximately one-third of patients (31.6%) had a family history of glaucoma, and approximately half had prior cataract surgery (OD 52.3% and OS 52.8%).

Ocular exam features were evaluated and compared across NDD groups. IOP was relatively low [average 14.5 mm Hg (SD 3.7) OD, average 14.3 mm Hg (SD 3.5) OS] and did not significantly differ across NDD groups (Table 2). The average visual acuity was 0.27 logarithm of minimal angle of resolution (logMAR) (SD 0.25) OD and 0.29 logMAR (SD 0.27) OS. APDs were uncommon overall [n = 2 (1.0%) OD, n = 8 (4.2%) OS]. APDs were most commonly seen in patients with CVA [n = 1 (4.6%) OD, n = 2 (9.1%) OS], although the difference was not statistically significant (p = 0.34 OD, p = 0.53 OS). The average CDR was 0.64 (SD 0.20) OD and 0.67 (SD 0.50) OS among all patients. Patients with coexistent MS and glaucoma had a smaller CDR [0.54 (SD 0.21) compared to other NDD groups [dementia 0.67 (SD 0.20), CVA 0.66 (SD 0.17), PD 0.64 (SD 0.19), and p = 0.01] in the right eye (OD).

Among the optic nerve features seen on the exam, cupping [*n* = 30 (15.1%) OD *n* = 32 (16.1%) OS], neuroretinal rim thinning [*n* = 45 (22.6%) OD *n* = 35 (17.6%) OS], pallor [*n* = 21 (10.6%) OD *n* = 26 (13.1%) OS], and peripapillary atrophy [*n* = 22 (11.1%) OD *n* = 25 (12.6%) OS] were observed most frequently (Fig. 1). Notching [*n* = 7 (3.5%) OD *n* = 3 (1.5%) OS], tilted discs [*n* = 5 (2.5%) OD *n* = 5 (2.5%) OS], and shallow disks [*n* = 4 (2.0%) OD *n* = 2 (1.0%) OS] were seen less frequently. Cupping was more common in patients with CVA [(*n* = 6 (27.3%)] compared to those with dementia [*n* = 18 (17.7%), MS (*n* = 1 (2.6%), or PD (*n* = 5 (13.9%), *p* = 0.048] in the OD. Similarly, pallor was more frequently seen in patients with CVA [*n* = 6 (27.3%)] and MS [(*n* = 9 (23.1%)] compared to patients with dementia [*n* = 6 (5.9%)] or PD [*n* = 5 (13.9%)], *p* = 0.007.

We found that zero patients in this study had a complete OCT, and there was a very high number of missing values (Table 3). The most highly missing variables were the OCT optic nerve features, including CDR, vertical CDR, disk area, and RNFL symmetry (Table 4). Similarly, zero patients had a VF test with complete data, and there

Table 1: Patient characteristics

Characteristic	*Patients (N = 199)*
Age, years	76.1 (13.6%)
Female	110 (55.3%)
Race	
Black	64 (32.3%)
White	126 (63.6%)
Other	8 (4.0%)
Hispanic	7 (3.6%)
NDD	
Dementia	
Alzheimer's dementia	18 (9.1%)
Vascular dementia	26 (13.1%)
Unspecified dementia	58 (29.2%)
CVA	22 (11.1%)
PD	36 (18.1%)
MS	39 (19.6%)
Family history of glaucoma	60 (31.6%)
Surgical history	
Cataract surgery OD	103 (52.3%)
Cataract surgery OS	104 (52.8%)
Traditional glaucoma surgery OD*	6 (3.0%)
Traditional glaucoma surgery OS*	10 (5.1%)
MIGS OD	2 (1.0%)
MIGS OS	2 (1.0%)

Data presented as mean (standard deviation) for continuous variables and *n* (percentage) for categorical variables; CVA, cerebrovascular accident; MIGS, minimally invasive glaucoma surgery; NDD, neurodegenerative disease; OD, right eye; OS, left eye; SD, standard deviation; *includes trabeculectomy and tube shunt surgery

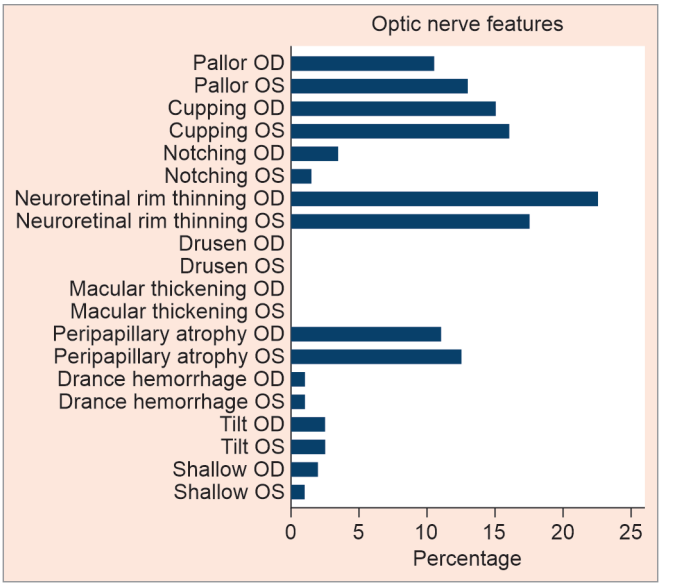


Fig. 1: Optic nerve features based on examination among all patients

Table 2: Ophthalmic exam findings across NDD diagnoses

Characteristic	*Dementia (N = 102)*	*CVA (N = 22)*	*MS (N = 39)*	*PD (N = 36)*	*All (N = 199)*	*p-value*
IOP OD, and mm Hg	14.2 (3.6)	13.6 (2.8)	15.4 (3.4)	14.9 (4.6)	14.5 (3.7)	0.17
IOP OS, and mm Hg	14.1 (3.8)	13.0 (3.0)	15.4 (3.0)	14.6 (3.4)	14.3 (3.5)	0.07
Visual acuity OD, logMAR	0.29 (0.22)	0.29 (0.20)	0.17 (0.26)	0.30 (0.31)	0.27 (0.25)	0.25
Visual acuity OS, logMAR	0.34 (0.30)	0.29 (0.32)	0.21 (0.25)	0.26 (0.18)	0.29 (0.27)	0.25
CCT OD, µm	546.7 (50.1)	536.2 (39.2)	553.7 (40.1)	543.7 (33.4)	546.4 (44.9)	0.67
CCT OS, µm	542.8 (41.8)	543.1 (41.1)	557.0 (41.5)	544.5 (28.7)	545.6 (39.8)	0.44
APD OD	1 (1.0%)	1 (4.6%)	0 (0%)	0 (0%)	2 (1.0)	0.34
APD OS	3 (3.0%)	2 (9.1%)	1 (2.7%)	2 (6.1%)	8 (4.2)	0.53
CDR OD	**0.67 (0.20)**	**0.66 (0.17)**	**0.54 (0.21)**	**0.64 (0.19)**	**0.64 (0.20)**	**0.01**
CDR OS	0.65 (0.20)	0.69 (0.18)	0.57 (0.20)	0.80 (1.08)	0.67 (0.50)	0.24
Lens						
Cataract OD	38 (37.6%)	5 (22.7%)	15 (38.5%)	13 (37.1%)	71 (36.0)	0.59
Cataract OS	36 (35.6%)	6 (27.3%)	14 (35.9%)	12 (33.3%)	68 (34.3)	0.89
Pseudophakic OD	**61 (60.4%)**	**16 (72.7%)**	**10 (25.6%)**	**19 (54.3%)**	**106 (53.8)**	**0.001**
Pseudophakic OS	**64 (63.4%)**	**15 (68.2%)**	**10 (25.6%)**	**23 (63.9%)**	**112 (56.6)**	**<0.001**

Data presented as mean (standard deviation) for continuous variables and Bold indicates statistical significance of *p* > 0.05, *n* (percentage) for categorical variables; APD, afferent pupillary defect; CCT, central corneal thickness; CDR, cup-to-disc ratio; CVA, cerebrovascular accident; IOP, intraocular pressure; logMAR, logarithm of minimal angle of resolution; MS, multiple sclerosis; OD, right eye; OS, left eye; PD, Parkinson's disease

Table 3: Percentage of patients with incomplete or absent OCT and VF tests

Characteristic	*Dementia (N = 102)*	*CVA (N = 22)*	*MS (N = 39)*	*PD (N = 36)*	*p-value*	*All (N = 199)*
Incomplete OCT, *n* (%)	80 (78.4%)	15 (68.2%)	30 (76.9%)	28 (77.8%)	0.78	153 (76.9%)
No OCT tests, *n* (%)	22 (21.6%)	7 (31.8%)	9 (23.1%)	8 (22.2%)	0.78	46 (23.1%)
Unable to complete OCT, *n* (%)	1 (1.0%)	2 (9.1%)	2 (5.1%)	1 (2.8%)	0.50	6 (3.0%)
Incomplete VF, *n* (%)	54 (52.9%)	13 (59.1%)	21 (53.9%)	22 (61.1%)	0.83	110 (55.3%)
No VF tests, *n* (%)	48 (47.1%)	9 (40.9%)	18 (46.2%)	14 (38.9%)	0.83	89 (44.7%)
Unable to complete VF, *n* (%)	2 (2.0%)	1 (4.6%)	0 (0%)	3 (8.3%)	0.46	6 (3.0%)

CVA, cerebrovascular accident; MS, multiple sclerosis; OCT, optical coherence tomography; PD, Parkinson's disease; VF, visual field

Table 4: OCT findings across NDD diagnoses

Characteristic	*Dementia (N = 102)*	*CVA (N = 22)*	*MS (N = 39)*	*PD (N = 36)*	*p-value*	*All (N = 199)*	*Missing*
CDR OD	0.69 (0.08)	–	0.69 (0.04)	0.70 (0.08)	0.97	0.69 (0.07)	190 (95.5%)
CDR OS	0.72 (0.08)	–	0.70 (0.01)	0.71 (0.05)	0.85	0.71 (0.05)	190 (95.5%)
Vertical CDR OD	0.85 (0.5)	–	0.65 (0.2)	–	0.44	0.74 (0.4)	190 (95.5%)
Vertical CDR OS	0.56 (0.3)	–	0.65 (0.1)	–	0.52	0.62 (0.2)	191 (96.0%)
Disc area OD, mm^2	**2.00 (0.3)**	**2.21 (0.6)**	**1.82 (0.3)**	**1.68 (0.2)**	**0.003**	1.94 (0.4)	133 (66.8%)
Disc area OS, mm^2	**1.96 (0.4)**	**2.36 (0.5)**	**1.83 (0.3)**	**1.76 (0.4)**	**0.02**	1.94 (0.4)	136 (68.3%)
Average thickness OD, µm	73.43 (15.0)	78.46 (17.4)	76.52 (14.7)	70.79 (13.9)	0.38	74.04 (15.0)	60 (30.2%)
Average thickness OS, µm	**74.72 (12.2)**	**64.33 (9.5)**	**78.48 (14.2)**	**69.87 (11.7)**	**0.002**	73.55 (12.9)	58 (29.1%)
RNFL symmetry	**89.7% (2.5%)**	–	**65.0% (0%)**	–	**0.01**	83.5% (12.5%)	195 (98.0%)
Superior quadrant OD							
Borderline	7 (6.9%)	1 (4.6%)	3 (7.7%)	2 (5.6%)	0.56	13 (6.5%)	74 (37.2%)
Thin	33 (32.4%)	6 (27.3%)	11 (28.2%)	16 (44.4%)		66 (33.2%)	
Nasal quadrant OD							
Borderline	3 (2.9%)	1 (4.6%)	3 (7.7%)	1 (2.8%)	0.56	8 (4.0%)	112 (56.3%)
Thin	4 (3.9%)	0 (0%)	0 (0%)	2 (5.6%)		6 (3.0%)	
Inferior quadrant OD							
Borderline	10 (9.8%)	0 (0%)	3 (7.7%)	1 (2.8%)	0.15	14 (7.0%)	81 (40.7%)
Thin	23 (22.6%)	3 (13.6%)	12 (30.8%)	13 (36.1%)		51 (25.6%)	
Temporal quadrant OD							
Borderline	4 (3.9%)	1 (4.6%)	3 (7.7%)	4 (11.1%)	0.23	12 (6.0%)	104 (52.3%)
Thin	8 (7.8%)	0 (0%)	7 (18.0%)	3 (8.3%)		18 (9.1%)	
Superior quadrant OS							
Borderline	**5 (4.9%)**	**0 (0%)**	**3 (7.7%)**	**1 (2.8%)**	**0.03**	9 (4.5%)	85 (42.7%)
Thin	**27 (26.5%)**	**13 (59.1%)**	**8 (20.5%)**	**13 (36.1%)**		61 (30.7%)	
Nasal quadrant OS							
Borderline	**1 (1.0%)**	**2 (9.1%)**	**4 (10.3%)**	**1 (2.8%)**	**0.005**	8 (4.0%)	122 (61.3%)
Thin	**3 (2.9%)**	**1 (4.6%)**	**0 (0%)**	**3 (8.3%)**		7 (3.5%)	
Inferior quadrant OS							
Borderline	**7 (6.9%)**	**1 (4.6%)**	**1 (2.6%)**	**1 (2.8%)**	**0.01**	10 (5.0%)	88 (44.2%)
Thin	**29 (28.4%)**	**12 (54.6%)**	**6 (15.4%)**	**13 (36.1%)**		60 (30.2%)	
Temporal quadrant OS							
Borderline	5 (4.9%)	1 (4.6%)	2 (5.1%)	0 (0%)	0.42	8 (4.0%)	108 (54.3%)
Thin	12 (11.8%)	4 (18.2%)	7 (18.0%)	4 (11.1%)		27 (13.6%)	

Data presented as mean (standard deviation) for continuous variables and Bold indicates statistical significance of $p > 0.05$, *n* (percentage) for categorical variables; CDR, cup-to-disc ratio; CVA, cerebrovascular accident; MS, multiple sclerosis; OCT, optical coherence tomography; OD, right eye; OS, left eye; PD, Parkinson's disease; RNFL, retinal nerve fiber layer

was a high number of missing values (Table 3). Pattern standard deviation, fixation losses, false negatives, and false positives were the most highly missing variables (Table 5). A small number of providers documented that patients were unable to undergo OCT and VF testing due to physical or attention limitations related to their NDD [*n* = 6 (3.0%), *n* = 6 (3.0%)].

Looking at the frequency of glaucoma testing in these patients, we found that the majority of patients received less than one OCT

per year, with 130 patients (65.3%) receiving zero OCTs per year and five patients (2.5%) receiving an average of <1/year (Fig. 2A). Further, the majority of patients also received less than the recommended number of one VF test per year with 145 patients (72.9%) receiving zero VF tests per year and nine patients (4.5%) receiving an average of less than one VF test per year (Fig. 2B).

For those with available OCT data, the average CDR was 0.69 (SD 0.07) OD and 0.71 (SD 0.05) OS (Table 4). Disk area was significantly higher among those with CVA [2.21 mm^2 (SD 0.6) OD 2.36 mm^2 (SD 0.5) OS] compared to those with dementia [2.00 mm^2 (SD 0.3) OD 1.96 mm^2 (SD 0.4) OS], MS [1.82 mm^2 (SD 0.3) OD 1.83 mm^2 (SD 0.3) OS] or PD [1.68 mm^2 (SD 0.2) OD 1.76 (SD 0.4) OS] in both eyes ($p < 0.05$ for both). Patients with CVA also had a thinner average RNFL thickness in the left eye (OS) [64.33 µm (SD 9.5)] compared to the other NDD groups [dementia 74.72 µm (SD 12.2), MS 78.48 µm (SD 14.2), and PD 69.87 µm (SD 11.7)], $p = 0.002$. In the OCT RNFL quadrant analysis, thinning was most frequently observed in the superior [$n = 66$ (33.2%) OD, $n = 61$ (30.7%) OS] and inferior [$n = 51$ (25.6%) OD, $n = 60$ (30.2%) OS] quadrants. CVA patients had significantly thinner superior and inferior quadrants in the OS compared to other NDD groups ($p < 0.05$ for all) (Table 4). Patients with PD had the highest proportion of nasal quadrant RNFL thinning compared to other NDDs ($p = 0.005$).

Among those with available VF data, the GHT was noted to be abnormal in 46 patients (23.1%) in the OD and 45 patients (22.6%) in the OS. CVA patients had a significantly higher proportion of abnormal GHTs in the OS [$n = 10$ (45.5%)] compared to those with dementia ($n = 25$, 24.5%), MS ($n = 5$, 12.8%), or PD ($n = 5$, 13.9%), $p = 0.01$. The average pattern standard deviation was 5.55 (SD 4.56) OD and 5.38 (SD 2.97) OS, although the number of pattern SD measurements was very small. Patients with MS had the lowest mean deviation scores, whereas patients with dementia and CVA had the highest mean deviation scores ($p < 0.05$) (Table 5). Fixation losses were common, with 30% (SD 27%) losing fixation in the OD and 34% (SD 28%) losing fixation in the left. When available, the average false positives and negatives were within reason (Table 5). There were no significant differences across groups for fixation losses, false positive, or false negative errors.

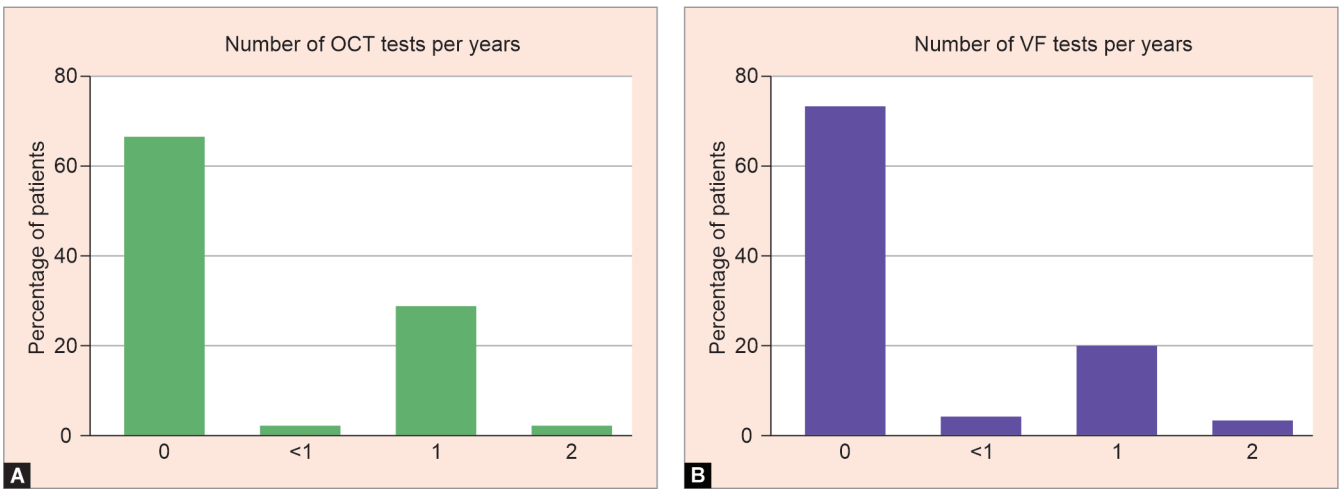
Discussion

In a study of 199 patients with coexistent POAG and NDD, we found a significant proportion of these patients had incomplete testing data that are necessary for proper diagnosis and monitoring of patients with glaucoma. In our study, zero patients had complete OCT or VF data, and the majority of variables from these tests were

Table 5: VF test findings across NDD diagnoses

Characteristic	*Dementia (N = 102)*	*CVA (N = 22)*	*MS (N = 39)*	*PD (N = 36)*	*p-value*	*All (N = 199)*	*Missing*
Abnormal GHT OD	25 (24.5%)	9 (40.9%)	7 (18.0%)	5 (13.9%)	0.23	46 (23.1%)	139 (69.9%)
Abnormal GHT OS	**25 (24.5%)**	**10 (45.5%)**	**5 (12.8%)**	**5 (13.9%)**	**0.01**	45 (22.6%)	143 (71.9%)
Pattern standard deviation OD	6.94 (4.75)	2.96 (0)	1.7 (0.37)	11.67 (0)	0.33	5.55 (4.56)	192 (96.5%)
Pattern standard deviation OS	6.71 (3.03)	4.61 (0)	2.06 (0.02)	7.49 (0)	0.31	5.38 (2.97)	191 (96.0%)
Mean deviation OD	**−9.72 (8.50)**	**−5.33 (7.55)**	**−3.46 (4.48)**	**−6.22 (8.92)**	**0.03**	−7.43 (8.23)	102 (51.3%)
Mean deviation OS	**−8.71 (6.44)**	**−16.71 (12.41)**	**−3.68 (2.52)**	**−9.26 (8.44)**	**<0.001**	−8.79 (7.99)	105 (52.8%)
Fixation losses OD	0.33 (0.26)	0.56 (0.51)	0.28 (0.19)	0.15 (0.23)	0.13	0.30 (0.27)	160 (80.4%)
Fixation losses OS	0.41 (0.27)	0.29 (0.50)	0.31 (0.23)	0.21 (0.29)	0.38	0.34 (0.28)	158 (79.4%)
False positives OD	0.07 (0.10)	0.25 (0.40)	0.09 (0.07)	0.19 (0.29)	0.19	0.11 (0.19)	156 (78.4%)
False positives OS	0.17 (0.50)	0.24 (0.38)	0.05 (0.05)	0.15 (0.28)	0.84	0.15 (0.39)	153 (76.9%)
False negatives OD	0.13 (0.08)	0.09 (0.16)	0.10 (0.10)	0.12 (0.11)	0.78	0.12 (0.10)	160 (80.4%)
False negatives OS	0.12 (0.10)	0.09 (0.09)	0.07 (0.06)	0.08 (0.08)	0.39	0.10 (0.09)	158 (79.4%)

Data presented as mean (standard deviation) for continuous variables and Bold indicates statistical significance of $p > 0.05$, *n* (percentage) for categorical variables; CVA, cerebrovascular accident; GHT, glaucoma hemifield test; MS, multiple sclerosis; OD, right eye; OS, left eye; PD, Parkinson's disease



Figs 2A and B: Number of OCT and VF tests per year

highly missing. Additionally, only 32% of patients were meeting the recommendation of at least one OCT per year, and 23% of patients met the recommendation of at least one VF per year.[3] This is not unexpected as these tests require active participation for perimetry, fundus photography, and optical coherence tomographic imaging; many patients with NDDs may have neurocognitive or physical limitations precluding their completion.[9,10] Patients in our study had a high proportion of fixation losses on VF testing, which may serve as evidence of their difficulty completing testing.

Beyond inhibiting the completion of glaucoma diagnostic testing, NDDs can also impact and confound the results of these tests. In our cohort, we found a thin, average RNFL as well as a significant proportion of patients with superior and inferior RNFL quadrant thinning. Although these findings are suggestive of glaucoma, they could also be due to NDD processes. RNFL thinning is known to occur in Alzheimer's disease, particularly in the superior and inferior quadrants, and is thought to be due to neuronal loss secondary to amyloid plaque deposition.[4,11–15] Similarly, the inflammation associated with MS is thought to cause neuronal death. RNFL thinning has been identified in MS patients with and without optic neuritis.[4,16–22] PD has also been associated with a significant reduction in RNFL thickness.[23–27] A study of 30 patients with PD followed over 5 years found significant progressive superotemporal and inferotemporal RNFL thinning compared to healthy controls.[28] CVA patients in our study had the thinnest average RNFLs compared to other NDDs, as well as a high proportion of thin RNFL quadrants in the OS. This finding of reduced RNFL thickness in CVA patients is consistent with what has been seen in previous studies and is hypothesized to be related to transneuronal retrograde degeneration, as well as hypoxia and hypoperfusion associated with strokes and atherosclerotic risk factors.[29–32] Because all of these NDDs cause RNFL thinning, this greatly complicates the ability to distinguish whether OCT changes are due to glaucoma or NDDs and calls into question the glaucoma diagnosis.

Among the perimetry results, the average mean deviation was −7.43 OD and −8.79 OS, and approximately 23% had an abnormal GHT. NDDs have also been shown to impact VF results in addition to OCT findings. In two studies of 79 eyes with Alzheimer's disease, mean deviation was significantly lower, pattern standard deviation (PSD) was significantly higher, and GHT was more frequently abnormal compared to healthy controls.[33] Additionally, two studies of 52 patients with PD alone found that pattern standard deviation and mean deviation were significantly worse compared to healthy controls, and 73% of eyes had an abnormal GHT.[34,35] Similarly, VF parameters have been shown to be impacted in patients with MS and prior strokes as well.[36–38] Thus, it is difficult to determine if abnormal VF findings in our study are due to glaucoma or NDDs themselves, which further complicates the glaucoma diagnosis.

In addition to impacting the results of glaucoma testing, NDDs can also alter the optic nerve appearance. In our study, we found that cupping, neuroretinal rim thinning, pallor, and peripapillary atrophy were the most common optic nerve findings, and the CDR was increased, consistent with what is typically seen in glaucoma. However, in studies of patients with MS, the optic nerve has been described to appear pale and atrophied, and patients with Parkinson's have been shown to have shallower cups compared to healthy controls.[39,40] Additionally, optic nerve pallor, increased CDR and cup volume, and decreased rim area have been reported in patients with Alzheimer's compared to healthy controls.[5,41]

These scenarios all expose flaws in our ability to diagnose glaucoma in patients with coexistent NDD. For example, it is possible that a patient with severe Alzheimer's disease may truly have glaucomatous optic neuropathy but may be unable to provide a VF and participate in an OCT to meet the structure–function criteria of the disease process. Our finding that zero patients had complete OCT or VF tests is evidence of the difficulty of obtaining adequate imaging in this patient population. Further, for those patients who can participate in VF and OCT testing, it is difficult to distinguish whether abnormal results are due to glaucoma or NDD. Even if the patient is definitively diagnosed with glaucoma, perhaps prior to the onset of severe NDD, subsequent follow-up may not provide much feedback for determination of progression and necessary changes in management, such as further IOP reduction. We suspect that ophthalmologists treating NDD patients diagnosed with glaucoma must most often rely on IOP. This can lead to difficult decisions for escalation of management in the absence of the perimetric or imaging data that help determine disease progression. In particular, glaucoma diagnosis could be exceedingly difficult in patients with coexistent glaucoma and NDD at low or normal IOP.

Our study is subject to multiple limitations. First, this was a single-center retrospective study, which limits the generalizability of our findings and introduces the possibility of confounding factors that we were unable to control for. Although missing data were an expected outcome of our study, the high degree of missing data may introduce bias in the VF and OCT values present. Refractive error data were not collected in this study. High refractive errors can impact testing results, which could affect our findings. Additionally, we were unable to determine the true baseline IOP in these patients since all patients had at least 3 years of follow-up with the IOP measurements taken from the most recent visits. It is likely that these patients were treated and that their baseline IOP is higher than what we found in this study. This will be controlled in a future prospective investigation. Further, VF testing in this study included both SITA standard and SITA fast, which could result in differing measurements. However, the purpose of this study was to assess what VF data are available to providers in practice when diagnosing glaucoma in patients with NDD. Additionally, since this study was retrospective and VF tests are often unavailable in these patients, including only SITA standard tests was not feasible. Finally, we did not collect detailed information on the type and timing of CVA. Since RNFL and VF changes related to CVA may change over time, this could impact our results.

Conclusion

In conclusion, we found that in a cohort of patients with NDD and coexistent glaucoma, only a small portion of patients received yearly OCT and VF testing. Of those who received testing, all patients had incomplete or missing OCT and VF values. We found RNFL thinning, VF defects, and optic nerve characteristics in our cohort that are consistent with glaucoma yet have also been associated with NDD, emphasizing the challenges of distinguishing these disease processes.

Clinical Significance

In this study, we highlight the difficulties of diagnosing and managing glaucoma in patients with coexistent NDD, given the inability to obtain adequate testing data and the potential for NDD to skew testing and exam findings. Providers may be forced to rely on IOP and other imperfect measures when diagnosing

glaucoma in patients with coexistent NDD. Further investigations are needed into how we can improve diagnosis and management in this complex patient population.

Funding

Kush Patel: NIH 2-T35-AG038047, UNC Chapel Hill National Training Center, Center for Aging & Health, MSTAR Program.

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