ORIGINAL RESEARCH

Factors Associated with 5-year Glaucomatous Progression in Glaucoma Suspect Eyes: A Retrospective Longitudinal Study

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Abstract

Purpose: Using demographic, clinical, visual field, and optical coherence tomography (OCT) variables to study the association of 5-year glaucomatous progression in glaucoma suspect eyes.

Patients and methods: This is a retrospective longitudinal clinical study. Inclusion criteria consisted of glaucoma suspect eyes (i.e., concerning cup-to-disk ratio and/or intraocular pressure (IOP) >21 mm Hg), age ≥ 30 years old, follow-up time of 5 years, best-corrected visual acuity (BCVA) of 20/100 or better, spherical equivalent (SE) higher than 8 diopters and an astigmatism less than 3 diopters. Eyes with glaucoma—determined by two consecutive, reliable visual field tests—were excluded, as well as any eyes with any clinically significant retinal or neurological disease. The percentage of glaucoma suspect eyes, which progressed to glaucoma within a 5-year period, was calculated. Study subjects were divided into the following groups: eyes that progressed to glaucoma and those that did not.

Results: In the 288 patients which we looked at, 365 total eyes, 323 eyes had concerning cup-to-disk ratio and 42 had ocular hypertension. Bivariate analysis showed that the eyes which progressed to glaucoma had significantly worse mean deviation, increased pattern standard deviation (PSD), and less visual field index (VFI). Our bivariate analysis also showed a thinner average, superior and inferior retinal nerve fiber layer thickness (RNFL), and more severe average, superior, and inferior RNFL damages (i.e., color grading scale) at baseline. Logistic regression analysis showed that only PSD and severe inferior RNFL damage (i.e., red color) to be significantly associated with 5-year glaucomatous progression.

Conclusion: Segmental RNFL damage and pattern standard deviation are associated with 5-year glaucomatous progression in glaucoma suspect eyes.

Keywords: Glaucomatous progression, Glaucoma suspect, Ocular hypertension, Optical coherence tomography (OCT), Retinal nerve fiber layer (RNFL), Risk factors, Visual field index, Visual field.

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Introduction

Glaucoma is a multifactorial progressive optic neuropathy, characterized by advanced neurodegeneration of the eye's retinal ganglion cells (RGCs) and their axons. This is determined by retinal nerve fiber layer (RNFL) attenuation, a specific pattern of damage to the optic nerve head, and visual field loss.[1,2] Different studies have shown that the development of glaucoma is correlated with several factors such as age,[1] glaucoma in one's family,[2] microvascular diseases (e.g., diabetes and hypertension),[3,4] vasospastic conditions (e.g., migraine),[5] myopia,[6] intraocular pressure (IOP),[1] and severity of visual field loss at diagnosis.[7] Improving our knowledge about factors that are associated with glaucomatous changes is crucial for earlier diagnosis of glaucoma. The significant factor in delaying vision loss due to glaucoma is its early diagnosis and treatment.[8] The United States Preventive Services Task Force (USPSTF) found insufficient evidence on the advantages of early glaucoma screening. However, the USPSTF did find evidence that treatment of IOP and early glaucoma lessens the number of individuals who develop small, clinically unnoticeable visual field defects. Meanwhile, there was evidence that the management of early asymptomatic primary open angle glaucoma reduces the number of individuals who experienced worsening visual field defects.[9]

In this study, we investigated the association of 5-year glaucomatous progression with several demographic, clinical, visual field, and optical coherence tomography (OCT) variables in glaucoma suspect eyes. Currently, there is limited data on using OCT parameters in the prediction of glaucomatous progression.

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Methods

Study Subjects

This 5-year retrospective study was performed at an inner city, tertiary care center and was approved by the Institutional Review Board at Wayne State University. Eyes who met the eligibility criteria were included in our study. Inclusion criteria were as follows: glaucoma suspect eyes defined as a concerning cup-to-disk

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ratio and/or intraocular pressure >21 mm Hg, age ≥30 years old, follow-up time of 5 years, best corrected visual acuity (BCVA) of 20/100 or better, spherical equivalent (SE) better than −8 diopters (D), and an astigmatism less than 3D. Eyes with glaucoma which were determined by at least two consecutive reliable visual field test results (24–2 Swedish Interactive Thresholding Algorithm [SITA] strategy, SITA–Fast; Humphrey Field Analyzer) and/or a pattern standard deviation (PSD) with *p*-value less than 0.05 were excluded. Our exclusion criteria strictly followed this definition, regardless of the appearance of the optic disk.[10] Furthermore, eyes with any significant retinal or neurological abnormalities were excluded. If both eyes of the same patient were eligible, both were included.

Study Outcomes

Glaucoma suspect eyes were divided into two groups; those which progressed to glaucoma vs those which did not (over 5-year follow-up). Table 1 shows the demographic, clinical, visual field and optical coherence tomography (OCT) characteristics of eyes included in our study. Visual field reliability was defined according to the manufacturer's criteria as fixation loss <20%, false-positive errors <15%, and false-negative errors <15%. We used quality Cirrus OCT scans, defined as scans with signal strength >6, and without any retinal nerve fiber layer (RNFL) diskontinuity, misalignment, involuntary saccade, or blinking artifacts. The OCT scans were within 6 months of the visual field tests. We calculated the percentage of glaucoma suspect eyes that progressed to glaucoma within a 5-year time period.

Statistical Analysis

Statistical analyses were performed using SAS Studio 3.5 (SAS Institute, Inc, Cary, North Carolina, USA), and *p*-value of <0.05 was considered statistically significant. The Kolmogorov-Smirnov test was used to verify the normal distribution of the study outcomes. Parametric and nonparametric statistics were used to compare different study outcomes between the study groups. Logistic regression analyses were performed on statistically significant study variables in the bivariate analysis to determine the association of 5-year glaucomatous progression with different factors.

Results

A total number of 365 eyes from 288 patients (323 eyes with concerning cup-to-disk ratio and 42 eyes with ocular hypertension) with mean age of 59.08 ± 11.24 years old were included in this study. Overall, 55 (15.07%) eyes progressed to glaucoma within average ± SD of 19.12 ± 4.23 months (Table 1). Table 1 shows bivariate analysis of different study variables between the study groups. Both study groups were statistically comparable with regard to age, sex, race, eye laterality, hypertension, diabetes mellitus, family history of glaucoma, fellow eye diagnosed with glaucoma, lens status, best-corrected visual acuity (BCVA), IOP, central corneal thickness, vertical cup-to-disk ratio, and cup-to-disk asymmetry ($p > 0.05$ for all; (Table 1). A total number of 48 (13.15%) eyes were on IOP-lowering medications at some point during the 5 years of follow-up (Table 1). There was no statistically significant difference between the study groups with regard to percentage of eyes on IOP-lowering medications ($p = 0.70$; Table 1) and mean number of medications ($p = 0.09$; (Table 1).

Compared to the eyes without progression, eyes with progression to glaucoma had statistically significantly worse MD ($p = 0.02$), higher PSD ($p < 0.01$) and less VFI ($p < 0.01$) at baseline (Table 1). Among them, only PSD showed statistically significant positive association with 5-year glaucomatous progression on logistic regression analysis (Table 2). Both groups were statistically comparable with regard to percentage of eyes with MD worse or better than -1dB ($p = 0.12$; Table 1). With regard to OCT parameters, there was no statistically significant difference between the study groups in terms of nasal and temporal RNFL thicknesses, cup volume, disk area and rim area at baseline ($p > 0.05$ for all; Table 1). The progressed group showed significantly thinner average, superior and inferior RNFL thicknesses ($p < 0.01$ for all; Table 1). While the progressed group had significantly more severe average, superior and inferior RNFL damages based on analysis of color grading scale ($p < 0.01$ for all), both study groups were statistically comparable with regard to severity of RNFL damage in nasal and temporal quadrants at baseline ($p > 0.05$ for all) (Table 1). Among those, the logistic regression analysis showed that only severe RNFL damage (i.e., red color) in the inferior quadrant was significantly associated with 5-year glaucomatous progression (Table 2). We found severe inferior RNFL damage (i.e., red color) has sensitivity, specificity, and positive and negative predictive values of 20.75%, 96.72%, 52.38%, and 87.28%, respectively.

Discussion

To successfully manage glaucoma, it is imperative to identify patients who are at higher risk of development and progression of glaucoma. This retrospective longitudinal study included 365 glaucoma suspect eyes of 288 patients. We investigated the association of several demographic, clinical, visual field and OCT variables with glaucomatous progression over a period of 5 years in a cohort of glaucoma suspect eyes.

Several studies including the Ocular Hypertension Treatment Study (OHTS)[1] and the European Glaucoma Prevention Study (EGPS)[11] have shown certain risk factors are predictive of the development of glaucoma. The OHTS has shown that baseline age, vertical and horizontal cup-to-disk ratio, PSD, and IOP were good predictors for the onset of primary open angle glaucoma (POAG) in ocular hypertensive patients.[1] In addition, central corneal thickness, measured by pachymetry, was found to be a powerful predictor for the development of POAG.[1] Furthermore, the OHTS has shown that the risk estimation for developing POAG in ocular hypertensive patients is equally accurate using IOP and central corneal thickness as measured, rather than applying a complicated adjustment formula to correct IOP for central corneal thickness.[12] Moreover, the OHTS has shown that optic disk hemorrhage is an independent predictive factor for development of POAG in patients with ocular hypertension.[13] Additionally, the EGPS has found that baseline age, vertical cup-to-disk ratio, vertical cup-to-disk ratio asymmetry, and PSD were strong predictors of the onset of open angle glaucoma in patients with ocular hypertension. Similar to the OHTS, the EGPS found central corneal thickness was a powerful predictor of the development of open angle glaucoma.[11]

In contrast to OHTS and EGPS, we did not find any significant association between age, central corneal thickness and cup-to-disk ratio, and 5-year glaucomatous progression. In our study, bivariate analysis showed that the glaucomatous progression group had significantly worse MD, higher PSD, and less VFI at baseline. However, only PSD showed statistically significant association with 5-year progression of glaucoma on the logistic regression analysis. We could not find any threshold for baseline MD that could significantly predict 5-year progression of glaucoma. For example, the study groups were not significantly different with regard to

Table 1: Demographic and baseline characteristics of study populations

	Total	*Progressed to glaucoma*	*Not progressed to glaucoma*	*p-value*
Number of eyes, n (%)	365	55 (15.07)	310 (84.93)	--
Number of patients, n (%)	288	50 (17.36)	238 (82.63)	--
Female: Male, n (%)	288	28 (56): 22 (44)	157 (66): 81 (34)	0.24^{+}
Race, n (%)				
African-American	240 (83.33)	41 (82.00)	199 (83.61)	0.44^{+}
Caucasian	37 (12.85)	6 (12.00)	27 (11.34)	
Other*	11 (3.82)	3 (6.00)	12 (5.04)	
Right: Left, n (%)	365	28 (51): 27 (49)	167 (54): 143 (46)	0.80^{+}
Age (years), mean ± SD	59.08 ± 11.24	59.08 ± 11.24	56.87 ± 11.96	0.23
Blood hypertension, n (%)				
Yes	204 (70.83)	41 (82.00)	163 (68.49)	0.08^{+}
No	84 (29.17)	9 (18.00)	75 (31.51)	
Diabetes mellitus, n (%)				
Yes	96 (32.98)	20 (40.00)	76 (31.93)	0.32^{+}
No	192 (67.02)	30 (60.00)	162 (68.07)	
Family history of glaucoma, n (%)				
Yes	126 (43.75)	23 (46.00)	103 (43.28)	0.84^{+}
No	162 (56.25)	27 (54.00)	135 (56.72)	
Fellow eye diagnosed with glaucoma, n (%)				
Yes	34 (9.32)	10 (18.18)	24 (7.74)	0.15^{+}
No	331 (90.68)	45 (81.82)	286 (92.26)	
Lens status (%)				
Phakic	257 (70.41)	39 (70.91)	218 (70.32)	0.13^{+}
Pseudophakic	108 (29.59)	16 (29.09)	92 (29.68)	
Time converted to glaucoma from baseline (months), mean ± SD		19.12 ± 4.23	--	--
BCVA, LogMAR, mean ± SD	0.083 ± 0.27	0.084 ± 0.17	0.083 ± 0.14	0.98^{++}
IOP (mm Hg), mean ± SD	18.07 ± 3.64	18.07 ± 3.64	17.24 ± 3.80	0.13^{++}
No. of eyes on medication (%)				
Yes	48 (13.15)	7 (12.73)	41 (13.23)	0.70^{+}
No	317 (86.85)	48 (87.27)	269 (86.77)	
No. IOP-lowering Medications	0.54 ± 0.63	0.47 ± 0.59	0.54 ± 0.58	0.09^{++}
CCT (microns), mean ± SD	540.25 ± 47.12	538.51 ± 52.10	542.20 ± 43.75	0.97^{++}
MD (dB), mean ± SD	-0.99 ± 1.59	-1.46 ± 2.02	- 0.91 ± 1.49	**0.02**$^{++}$
MD (dB) ≤ -1dB, n (%)				
Yes	148 (40.55)	28 (50.91)	120 (38.71)	0.12^{+}
No	217 (59.45)	27 (49.09)	190 (61.29)	
PSD, mean ± SD	1.42 ± 0.20	1.50 ± 0.21	1.40 ± 0.20	**<0.01**$^{++}$
VFI, mean ± SD	99.06 ± 1.00	98.71 ± 1.20	99.12 ± 0.95	**<0.01**$^{++}$
Vertical C/D ratio, mean ± SD	0.60 ± 0.15	0.61 ± 0.17	0.60 ± 0.11	0.59^{++}
C/D asymmetry, mean ± SD	0.10 ± 0.11	0.11 ± 0.12	0.10 ± 0.11	0.70^{++}
Average RNFL thickness (micron), mean ± SD	86.73 ± 11.72	83.39 ± 14.41	88.34 ± 9.98	**<0.01**$^{++}$
Inferior RNFL thickness (micron), mean ± SD	112.67 ± 17.82	105.67 ± 22.66	114.54 ± 16.52	**<0.01**$^{++}$
Nasal RNFL thickness (micron), mean ± SD	68.67 ± 13.11	67.65± 14.48	69.59 ± 12.86	0.32^{++}
Superior RNFL thickness (micron), mean ± SD	108.42 ± 20.27	103.11 ± 25.84	110.74 ± 16.77	**<0.01**$^{++}$
Temporal RNFL thickness (micron), mean ± SD	57.50 ± 11.47	56.65 ± 12.30	58.17 ± 10.54	0.34^{++}
Cup volume (mm^3), mean ± SD	0.33 ± 0.23	0.33 ± 0.26	0.33 ± 0.22	0.92^{++}
Disk area (mm^2), mean ± SD	2.07 ± 0.41	2.10 ± 0.45	2.05 ± 0.40	0.45^{++}

Continued...

Table 1: *Continued*

	Total	*Progressed to glaucoma*	*Not progressed to glaucoma*	*p-value*
Rim area (mm^2), mean ± SD	1.20 ± 0.27	1.20 ± 0.34	1.20 ± 0.23	0.96^{++}
Average RNFL color, n (%)				
White	18 (4.93)	4 (7.27)	14 (4.52)	**<0.01**$^{+}$
Green	285 (78.08)	37 (67.27)	248 (80.00)	
Yellow	49 (13.42)	7 (12.73)	42 (13.55)	
Red	13 (3.56)	7 (12.73)	6 (1.93)	
Inferior RNFL color, n (%)				
White	17 (4.66)	1 (1.85)	16 (4.61)	**<0.01**$^{+}$
Green	295 (80.82)	37 (72.22)	258 (83.88)	
Yellow	31 (8.49)	5 (5.56)	26 (8.22)	
Red	22 (6.03)	12 (20.37)	10 (3.30)	
Nasal RNFL color, n (%)				
White	25 (6.85)	4 (7.27)	21 (6.77)	0.52^{+}
Green	323 (89.31)	48 (87.27)	275 (88.71)	
Yellow	11 (3.01)	1 (1.82)	10 (3.23)	
Red	6 (1.64)	2 (3.64)	4 (1.29)	
Superior RNFL color, n (%)				
White	21 (5.75)	6 (10.91)	15 (4.84)	**<0.01**$^{+}$
Green	290 (79.45)	33 (60.00)	257 (82.90)	
Yellow	25 (6.85)	6 (10.91)	19 (6.13)	
Red	29 (7.94)	10 (18.18)	19 (6.13)	
Temporal RNFL color, n (%)				
White	10 (2.74)	2 (3.64)	8 (2.58)	0.31^{+}
Green	305 (83.56)	42 (76.36)	263 (84.83)	
Yellow	28 (7.67)	6 (10.91)	22 (7.10)	
Red	22 (6.03)	5 (9.09)	17 (5.48)	

$^{+}$Chi square test; $^{++}$t test; BCVA, best-corrected visual acuity; IOP, intraocular pressure; CCT, central corneal thickness; RNFL, retinal nerve fiber layer; C/D ratio, cup to disk ratio; MD, mean deviation; PSD, pattern standard deviation; SD, standard deviation; VFI: visual field index

percentage of eyes with baseline MD worse or better than -1dB (Table 1). The majority of glaucoma suspicious eyes in our study were based on optic nerve appearance. Therefore, findings of the OHTS and EGPS may not be comparable with our findings.

Structural and functional changes are useful indicators to detect glaucoma progression, but these changes often do not happen simultaneously over a period of time. However, both structural and functional progression will ultimately confirm the findings of the other modality during the course of follow-up. There is still controversy regarding whether structural changes precede functional loss as measured by perimetry.[14-23] Although studies have different definitions for structural and functional progression, some studies have reported that structural changes precede functional changes in glaucoma progression.[14,24,25] The OHTS has shown that 35% of patients with visual field loss were without any sign of structural progression.[8] Medeiros et al.[25] and Sehi et al.[14] have similarly reported that 34% and 37% of all glaucoma suspect individuals, respectively, developed visual field defects without structural progression. It is not quite clear why functional progression precedes structural progression in some patients and vice versa. In our study, we found eyes in the progressed group have significantly thinner baseline average, superior and inferior RNFL thicknesses in bivariate analysis. However, the logistic regression analysis did not show any significant association between average, superior, and inferior RNFL thicknesses and 5-year progression of glaucoma (Table 2). In bivariate analysis, we found that the progressed group had significantly more severe average, superior, and inferior RNFL damage based on the color grading scale at baseline. However, the logistic analysis showed only severe inferior RNFL damage was significantly associated with 5-year glaucomatous damage (Table 2). We found severe inferior RNFL damage (i.e., red color) has a very high specificity of 96.72% Taliantzis et al. have shown that segmental RNFL thickness on OCT examination constitutes an important indication of early functional changes, even if they are not still manifested on achromatic perimetry.[24] Lalezary et al. found that OCT RNFL measurements at baseline was an independent predictor for development of glaucomatous change in glaucoma suspect/preperimetric glaucoma and glaucomatous eyes. They reported that average and superior RNFL are significant predictors of subsequent visual field loss.[26] They found that for every 10 µm decrease in average RNFL there is an associated 38% higher chance for visual field progression; meanwhile, for every 10 µm thinning of superior RNFL, there is associated 20% higher chance of visual field progression.[26]

Our study has potential limitations. Due to the retrospective nature of the study, eyes participated in this study were diagnosed at the discretion of the attending physician. This may make it difficult to determine the true 5-year progression of glaucoma. The

Table 2: Association of progression to glaucoma with different study outcomes: Logistic Regression Analysis

	Coefficient ± SE	*p-value*	*95% CI*
Baseline MD (dB)	–0.08 ± 0.40	0.55	0.70, 1.21
Baseline PSD	2.77 ± 1.16	**0.01**	1.64, 2.52
Baseline VFI	0.10 ± 0.26	0.69	0.66, 1.86
Baseline inferior RNFL thickness (micron)	–0.01± 0.02	0.76	0.95, 1.04
Baseline superior RNFL thickness (micron)	–0.03 ± 0.02	0.11	0.93, 1.01
Baseline average RNFL thickness (micron)	–0.01 ± 0.05	0.85	0.90, 1.09
Baseline average RNFL color			
White	Reference		
Green	–1.86 ± 0.93	0.14	- 0.07, 0.97
Yellow	–1.16 ± 0.73	0.11	- 0.02, 1.20
Red	–1.14 ± 0.64	0.09	- 0.01, 1.11
Baseline inferior RNFL color			
White	Reference		
Green	1.26 ± 1.16	0.35	0.36, 34.13
Yellow	1.34 ± 1.34	0.30	0.28, 53.03
Red	3.62 ± 1.35	**0.03**	2.64, 53.99
Baseline superior RNFL color			
White	Reference		
Green	–1.76 ± 0.67	0.14	–0.08, 1.16
Yellow	–1.11 ± 0.84	0.89	0.21, 5.85
Red	–1.62 ± 1.15	0.93	0.17, 6.69

RNFL, retinal nerve fiber layer; MD, mean deviation; PSD, pattern standard deviation; SE, standard error; VFI, visual field index

majority of participated subjects in our study included glaucoma suspect eyes based on suspicious optic nerve appearance. This makes it difficult to compare our results with those of OHTS and EGPS where the majority of their subjects had glaucoma suspect eyes based on ocular hypertension. In addition, 83.33% of study population were African American which may make it difficult to generalize our results to other ethnicities.

CONCLUSION

In conclusion, we found that severe baseline inferior RNFL damage and PSD were significantly associated with 5-year glaucomatous progression in glaucoma suspect eyes. We suggest that these eyes should be considered to be at a higher risk of glaucomatous progression. In addition, severe inferior RNFL damage has a specificity of 96.72%. Decisions on the implementation and extent of treatment for glaucoma suspect eyes can be difficult and need an understanding of important risk factors for development and progression of glaucoma. Further studies are warranted to determine the importance of different risk factors including genetic factors in glaucoma suspect eyes particularly those with suspicious optic nerve appearance. Currently, there is a lack of cohort studies determining the risk factors for glaucomatous progression in glaucoma suspects eyes based on optic nerve appearance.

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